Physical activity and exercise capacity in survivors of preterm birth

A population-based cohort study of long-term consequences of prematurity

Mette Engan

Thesis for the degree of Philosophiae Doctor (PhD)
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Scientific environment

The research work presented in this thesis was conducted as part of the PhD programme at the Department of Clinical Science, Faculty of Medicine, University of Bergen, Bergen, Norway. The research was carried out within the framework of the Project Extreme Prematurity and the Inducible Laryngeal Obstruction (ILO) group, which are affiliated to WestPaed Research; a scientific environment evolved from the Children and Youth Clinic at Haukeland University Hospital, Bergen, Norway.

Collaborating partners include the Department of Paediatric and Adolescent Medicine at Stavanger University Hospital, Norway and the Department of Health and Functioning, Western Norway University of Applied Sciences, Bergen, Norway.

The primary supervisor for this PhD project was paediatrician and associate professor Hege Synnøve Havstad Clemm, with paediatrician and associate professor Maria Vollsæter, paediatrician and professor Thomas Halvorsen, and physiotherapist and professor Ola Drange Røksund as co-supervisors.

Statistical analyses were performed in collaboration with biostatistician and professor Geir Egil Eide and biostatistician Karl Ove Hufthammer from the Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway.

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Abstract

Background

Physical activity (PA) is an important mediator of health. Extremely preterm (EP) (<28 weeks' gestation) and extremely low birth weight (ELBW) (<1000 g) subjects are at increased risk of long-term sequelae that may influence their participation in physical activity (PA) and their exercise capacity.

Aims

To compare PA and exercise capacity, by measuring peak oxygen consumption (VO_2), as well as body composition between EP/ELBW-born subjects and term-born (TB) controls. Another aim was to identify factors associated with poorer outcomes related to participation and performance in PA and exercise capacity in the EP/ELBW-born group.

Cardiopulmonary exercise testing (CPET) both with and without continuous laryngoscopy were used for assessing peak VO_2. A method comparison study was therefore conducted to investigate the reliability of peak VO_2 obtained by CPET performed with continuous laryngoscopy (CLE test), compared to standard CPET.

Methods

A Norwegian national cohort of EP/ELBW children born during 1999-2000 and a regional sub-sample of that cohort and their TB controls were studied. At age 5 years, EP/ELBW-born children were assessed to identify motor- and behavioural problems, as well as deficits in intellectual functioning. At age 11 years, body composition was determined by dual-energy X-ray absorptiometry, and information on PA participation and performance was obtained from a parental questionnaire.

A sub-group of particular interest comprising EP/ELBW-born adults who underwent neonatal patent ductus arteriosus (PDA) surgery were examined for left vocal cord paralysis (LVCP). In this PDA surgery group, peak VO_2 measurements were obtained and laryngeal obstruction during exercise was assessed for by using the CLE test. The results on peak VO_2 were compared to EP/ELBW-born controls with no history of PDA

surgery, as well as to TB controls who underwent ordinary CPET. The reliability of gas exchange parameters obtained by the CLE test was determined by comparing gas exchange variables in healthy subjects performing CPET both with and without added CLE setup.

Results

EP/ELBW-born children and young adults were less often physically active than TB controls. Parental reported data showed that EP/ELBW-born children had reduced endurance and poorer proficiency in sports and play and were less vigorous during PA than TB controls. EP/ELBW-born children with neurodevelopmental disability (NDD) had even poorer PA outcomes. Young EP/ELBW-born adults had reduced peak VO_2 compared to TB controls with a mean difference (95% confidence interval (CI)) of 4.9 (1.8– 8.0) ml/kg/min.

In otherwise healthy EP/ELBW-born children, preschool motor coordination problems, behavioural problems, and borderline intellectual functioning predicted lower endurance and less vigorous PA at school age. Additionally, motor coordination problems and behavioural problems predicted poor proficiency in sports activities, and borderline intellectual functioning predicted fine motor clumsiness (odds ratios 2–5).

Compared to TB controls, EP/ELBW-born children had lower values (mean difference, 95% CI) for total bone mineral density z-score (0.30, 0.13–0.52), muscle mass (0.9, 0.3–1.5 kg), and fat mass ratio (0.14, 0.06–0.21). The differences were reduced when adjusting for PA frequency. The positive association between PA frequency and bone mineral density and muscle mass was weaker in EP/ELBW-born children compared to TB controls.

The prevalence of LVCP in 30 EP/ELBW-born adults who underwent PDA surgery was 53%. LVCP and observed laryngeal obstruction during exercise in the PDA surgery group were not associated with reduced peak VO_2.

Agreement (±95% limits of agreement) for peak VO_2 when obtained by the CLE test and standard CPET was 0.2 (±3.7) ml/kg/min.

Conclusions and future perspectives

This thesis found that EP/ELBW-born children and young adults were less physically active and that they had lower peak VO_2 as adults, compared to TB controls. Children born EP/ELBW with NDD, motor coordination problems, behavioural problems, or borderline intellectual functioning had poorer outcomes related to later PA performance. These findings highlight the need for focused intervention in these groups to improve PA outcomes. The body composition profile in EP/ELBW-born children implies an increased risk of cardiometabolic disease and osteoporosis later in life. High prevalence of LVCP after neonatal PDA surgery has implications in terms of follow-up, although LVCP was not associated with reduced peak VO_2. Peak VO_2 obtained by the CLE test can be used interchangeably with peak VO_2 obtained from standard CPET. Future studies should aim to determine factors that enhance PA participation in EP/ELBW-born individuals and to investigate short- and long-term health benefits of PA in the EP/ELBW-born population.

List of publications

Paper I

Engan M, Vollsæter M, Øymar K, Markestad T, Eide GE, Halvorsen T, Juliusson P, Clemm H. Comparison of physical activity and body composition in a cohort of children born extremely preterm or with extremely low birth weight to matched term-born controls: a follow-up study. *BMJ Paediatr Open*. 2019 Jun 29;3(1):e000481.

Paper II

Engan M, Engeseth MS, Fevang S, Vollsæter M, Eide GE, Røksund OD, Halvorsen T, Clemm H. Predicting physical activity in a national cohort of children born extremely preterm. *Early Hum Dev*. 2020 Jun;145:105037.

Paper III

Engan M, Engeset MS, Sandvik L, Gamlemshaug OCO, Engesæter IØ, Øymar K, Vollsæter M, Røksund OD, Hufthammer KO, Halvorsen T, Clemm HH. Left vocal cord paralysis, lung function and exercise capacity in young adults born extremely preterm with a history of neonatal patent ductus arteriosus surgery – a national cohort study. *Front Pediatr*. 2022 Jan 3;9:780045.

Paper IV

Engan M, Hammer IJ, Bekken M, Halvorsen T, Fretheim-Kelly ZL, Vollsæter M, Bovim LPV, Røksund OD, Clemm H. Reliability of maximum oxygen uptake in cardiopulmonary exercise testing with continuous laryngoscopy. *ERJ Open Res*. 2021 Feb 15;7(1):00825-2020.

Abbreviations

AGA	appropriate for gestational age
ALM	appendicular lean mass
ALMI	appendicular lean mass index
%BF	percentage of body fat
BMC	bone mineral content
BMD	bone mineral density
BMDth	total hip bone mineral density
BMI	body mass index
BPD	bronchopulmonary dysplasia
BW	birthweight
CI	confidence interval
CLE	continuous laryngoscopy during exercise
CO_2	carbon dioxide
CoV	coefficient of variation
CP	cerebral palsy
CPAP	continuous positive airway pressure
CPET	cardiopulmonary exercise testing
DCD	developmental coordination disorder
DXA	dual-energy X-ray absorptiometry
ELBW	extremely low birthweight
EP	extremely preterm
FEV_1	forced expiratory volume in 1 second
FiO_2	fraction of inhaled oxygen
FIQ	full-scale intelligence quotient
FM	fat mass
FMI	fat mass index
FVC	forced vital capacity
GA	gestational age
GMFCS	gross motor function classification system

HELLP	haemolysis, elevated liver enzymes, and low platelets
HR	heart rate
ICC	intraclass correlation coefficient
IQ	intelligence quotient
LBM	lean body mass
LBMI	lean body mass index
LoA	limits of agreement
LRL	left recurrent laryngeal
LVCP	left vocal cord paralysis
MABC	Movement Assessment Battery for Children
NDD	neurodevelopmental disability
NEC	necrotising enterocolitis
NICU	neonatal intensive care unit
OR	odds ratio
PA	physical activity
PDA	patent ductus arteriosus
PVL	periventricular leukomalacia
RDS	respiratory distress syndrome
RER	respiratory exchange ratio
ROP	retinopathy of prematurity
RQ	research question
RR	respiratory rate
SD	standard deviation
SDQ	Strengths and Difficulties Questionnaire
SGA	small for gestational age
STR	subscapular-to-triceps skinfold ratio
TB	term-born
TDS	Total Difficulties Score
TDS90	TDS ≥90th percentile
T_i/T_{tot}	inspiratory time to total time of the breathing cycle
VCO_2	carbon dioxide production

VE	minute ventilation
VLBW	very low birthweight
VO_2	oxygen consumption
VO_2%	peak oxygen consumption as a percentage of the reference
VP	very preterm
Vt	tidal volume
WHtR	waist-to-height ratio
WPPSI-R	Wechsler Preschool and Primary Scale of Intelligence-revised
ws	within subject

Contents

1. GENERAL INTRODUCTION

Major progress in antenatal and neonatal intensive care medicine over the past four decades has led to improved prospects of survival for neonates born extremely preterm (EP) (<28 weeks' gestation) or with extremely low birthweight (ELBW) (<1000 g) [1-3]. Preterm birth from the protected intrauterine environment implies that important stages of human organ development and maturation must continue in a neonatal intensive care unit (NICU). Survival usually requires comprehensive intensive care interventions, including assisted ventilation and long periods of oxygen supplementation, which themselves may be harmful to the preterm neonate. Lifelong consequences of this biological challenge are mainly unknown—high survival rates have been achieved only recently and the oldest survivors are still young adults.

Large cohorts of EP/ELBW-born infants are now growing up. From a public health perspective, efforts should focus on maintaining their health throughout life. According to recent literature, it is becoming increasingly clear that preterm-born adults are at risk of a range of non-communicable diseases, and even premature death [4-9]. However, studies performed in the general populations have shown that non-communicable diseases can be modified by physical activity (PA) [10,11]. It is therefore of concern that EP/ELBW-born individuals tend to be less physically active than their term-born (TB) peers [12-17]. In this context, it is important to study PA in preterm-born children and adults and to identify those subgroups more prone to physical inactivity.

Thus, the overall aim of this study was to examine long-term consequences of prematurity, with a focus on factors important for PA and exercise capacity in survivors of EP/ELBW birth.

2. INTRODUCTION TO PREMATURITY

2.1 Preterm birth

2.1.1 Definition and terminology

Normal pregnancy lasts 40 weeks, counting from the first day of the mother's last menstrual period. The gestational age (GA) is estimated more reliable by foetal biometric measurements obtained by ultrasonography performed before 22 weeks' gestation [18]. Preterm birth is defined as any birth that occurs before 37 weeks, or 259 days, of pregnancy and is further classified according to GA as shown in Table 1 [19]. The neonate's birth weight (BW) is commonly classified as *small*, *appropriate*, or *large* for GA according to BW by GA [20,21]. In addition, BW is also labelled *very low* (< 1500 g) or *extremely low* (< 1000 g) regardless of GA or weight percentiles.

2.1.2 Epidemiology

Approximately 15 million infants (11% of all newborns) are born prematurely every year, and worldwide, preterm birth complications are the leading cause of death in children under five years of age. The incidence of preterm birth varies across countries, ranging from 5% of all newborns in Europe to 13% in North Africa [22]. In Norway, the incidence of preterm birth has been between 5.5% to 6.8% in the last 20 years (2000–2020), where 0.3–0.5% were born EP [23].

Table 1 Classification of prematurity based on gestational age

Label	Definition
Extremely preterm	<28 weeks of completed gestation
Very preterm	28 to <32 weeks of completed gestation
Moderate preterm	32 to <34 weeks of completed gestation
Late preterm	34 to <37 weeks of completed gestation
Term	37 to <42 weeks of completed gestation
Post-term	>42 weeks of completed gestation

2.1.3 Preterm birth and neonatal mortality

Progress in neonatal medicine over the last decades has led to improved survival, most notable among the smallest and most immature infants whose survival depends on advanced neonatal intensive care [1-3]. In the early 1960s, less than 10% of ELBW neonates survived, while from the 1990s, this number seems to stabilize above 60%. The same trend has been observed among very low birthweight (VLBW) neonates, with improved survival rates from 50% to 90% during the same time span [2]. A study on a Norwegian cohort of children born EP in 2012–14 found survival rates of 18% at 22 weeks, 29% at 23 weeks, 56% at 24 weeks, 84% at 25 weeks, and 90% at 26 weeks' gestation [24]. The research presented in this thesis was based on a cohort of EP/ELBW-born infants in Norway with similar survival rates [3].

2.1.4 Risk factors for preterm birth

Several risk factors for preterm birth have been reported, some related to the mother, some to the placenta, and some to the foetus. Two-thirds of preterm births are spontaneous, which include spontaneous preterm labour and preterm birth following preterm rupture of chorioamniotic membranes. The remaining third comprises those preterm births induced before labour for maternal or fetal indication [25-27]. Common maternal indications for induced preterm birth include HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome, pre-eclampsia, and eclampsia. Common fetal indications include intrauterine growth restriction, poor umbilical blood flow, placental abruption, placenta previa, and intrauterine infection [25]. Many socio-demographic, nutritional, medical, obstetric, and environmental factors have been shown to increase the risk of spontaneous preterm birth [25-27]. However, the aetiology is not fully understood, and most preterm births have no associated risk factors [25].

2.1.5 Born too soon: impact on organ development and neonatal morbidity

Preterm birth represents a disruption of the continuous intrauterine fetal maturation, exposing the immature organs to the extrauterine environment. In this setting, both anatomical and functional development of the organs is incomplete, with the brain, respiratory, digestive, and circulation systems being particularly vulnerable.

Common neonatal morbidities are respiratory problems, intracerebral haemorrhage, bacterial infections, necrotising enterocolitis (NEC), poor temperature and blood sugar regulation, retinopathy of prematurity, and feeding difficulties [3,28]. Neonatal complications, morbidity, and mortality increase with decreasing GA [3]. Intrauterine exposures prior to birth may also increase the risk of short and long-term illness [29].

In high-income countries, the rate of neurodevelopmental impairment among children born EP increases with reduced numbers of completed weeks of gestation, ranging from approximately 30% for those born at 27 weeks of GA to 80% for those born at 22 weeks of GA [30]. Thus, premature birth bears life-long public health significance and representing considerable economic costs to the health services, as well as to families and caregivers [31].

Fetal pulmonary development

The foetal lung develops from the primitive lung bud early in embryonic life. Subsequent morphological changes under the control of genetic, hormonal, and environmental factors ultimately lead to the development of a lung capable of respiration and gas exchange at term [32]. About 15–30% of alveoli are formed at term and alveolar formation continues at least until the child is 2–3 years old [32]. At 23–24 weeks' gestation, the conducting airways are fully formed, and thin-walled terminal saccules are established, which constitutes the respiratory component of the lung. At this stage, the primitive blood-air barrier is thick, and gas transport therefore limited. From around 26 weeks' gestation, type II pneumocytes start producing surfactant, which lines the alveolar air-liquid interface and facilitates lung expansion, thus reducing work of breathing. This surfactant is not secreted into the airway lumen before around 30 weeks' gestation [32].

Lung disease in infancy

Most EP newborns present a clinical picture of increased work of breathing with chest retractions, grunting, tachypnoea, and cyanosis—a condition known as respiratory distress syndrome (RDS) caused by lack of surfactant, poor lung compliance, and immature gas exchange units [33]. Ventilatory support and supplemental oxygen are necessary to maintain adequate gas exchange in newborns with RDS.

Bronchopulmonary dysplasia (BPD) describes a form of chronic lung disease in preterm infants born earlier than 32 weeks' gestation who are dependent on prolonged oxygen supplementation beyond 28 days postnatally. The severity of BPD is further classified at 36 weeks' gestation or at discharge to home, whichever comes first, into mild (no oxygen supplementation), moderate (fraction of inhaled oxygen (FiO_2) <0.30), or severe (FiO_2 ≥0.30 or requiring positive pressure ventilation) [34].

BPD remains the most common complication associated with EP birth, with an incidence of 10–20% among infants born at 27–28 weeks' gestation and 60–80% among those born at 23–24 weeks' gestation [35,36]. BPD is recognised to result from an aberrant reparative response to both antenatal and repetitive postnatal injury to the developing lungs [37]. This leads to reduced alveolar septation with fewer and larger alveoli, as well as abnormal microvasculature development resulting in increased pulmonary vascular resistance. Life-saving measures such as oxygen therapy and mechanical ventilation have been associated with BPD [38,39]. Both inflammation and growth arrest probably play a central role in the development of BPD, although the pathophysiology of BPD remains poorly understood [40].

Early cardiovascular consequences of preterm birth

Preterm birth causes an early transition from a lower-resistance placental circulation during fetal development to higher-resistance and relative hyperoxic ex-utero environment [41]. In preterm-born neonates, cardiac remodelling with disproportionate cardiac hypertrophy accompanied by reduced left ventricular diastolic function has been demonstrated [42]. The long-term effect of this cardiac remodelling needs further evaluation.

Patent ductus arteriosus

Patent ductus arteriosus (PDA) is the most common cardiovascular condition affecting premature neonates and is diagnosed in 40–70% of VLBW and ELBW neonates, respectively [43,44]. PDA is a persistent vascular fetal shunt between the descending aorta and the main pulmonary artery that may give rise to cardiovascular dysfunction with increased pulmonary blood flow and systemic hypoperfusion. Neonatologists rely on

echocardiographic assessment and clinical signs to diagnose a haemodynamically significant PDA[45] which is associated with worsening of lung disease, prolonged mechanical ventilation, and an increased risk of pulmonary haemorrhage, NEC, and intraventricular haemorrhage [46]. Treatment options include a conservative symptomatic approach, pharmacological intervention, or surgical ligation, with the latter option commonly reserved for critically ill patients requiring extensive respiratory support when medical treatment has failed or is contraindicated [43,47].

The left and right recurrent laryngeal nerves control the intrinsic muscles of the larynx which are responsible for movement of the vocal cords that are necessary for phonation and protection of the lower airway during swallowing. The principal intrinsic laryngeal muscle responsible for vocal cord opening (abduction) is the posterior cricoarytenoid muscle, which is important for the synchronised dilatation of the glottis seen with inspiration [48]. The left recurrent laryngeal (LRL) nerve is anatomically closely related to the ductus arteriosus (Figure 1). Open surgical closure of PDA in preterm-born neonates may lead to injury of the LRL nerve with subsequent left vocal cord paralysis (LVCP) (Figure 2, and Paper III, Figure 5) [49]. Affected neonates may present with stridor, weak cry, aspiration and feeding problems [50,51].

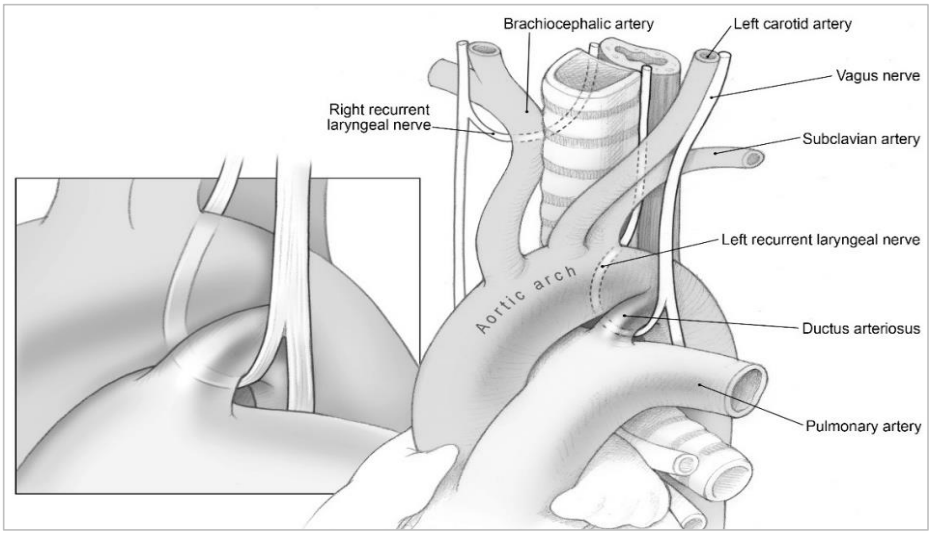

Figure 1 Anatomy of the left recurrent laryngeal nerve. Printed with permission from Christine Gralapp, MA, CMI Medical Illustration Fairfax, CA.

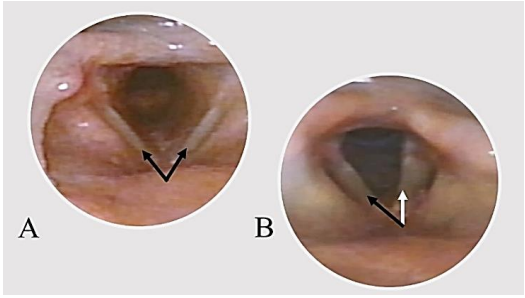

Figure 2 Left vocal cord paralysis. (**A**) Vocal cords normally abducted during inspiration (black arrows). (**B**) Paralysed left vocal cord in a para-median position, unable to abduct as normal during inspiration (white arrow).

Development of the brain and nervous system

Formation of the brain and nervous system starts in the third week of fetal development and continuous through the fetal life. Normal brain development is a complex process of micro- and macro-structural events including neuronal and glial proliferation and migration, myelination, and organizational development of cortical layers and circuits. Both gene expression and environmental input are important for normal brain development [52].

Cerebral complications in the preterm infant

Peri- and intraventricular haemorrhage and periventricular leukomalacia (PVL) are the most important acquired brain lesions of VP- and EP-born neonates [53]. The pathogenesis of peri- and intraventricular haemorrhage is likely multifactorial and is associated with RDS, impaired cerebral blood flow regulation, and inflammation [54,55]. The incidence of peri- and intraventricular haemorrhage is about 20% among VLBW infants and 25–30% among ELBW infants [53,56].

PVL refers to ischemic infarcts in cerebral white matter, with focal and diffuse components. PVL has been associated with neuronal/axonal diseases affecting the cerebral white matter, thalamus, basal ganglia, cerebral cortex, brainstem, and cerebellum. This constellation of brain abnormalities is termed 'encephalopathy of prematurity' [57]. Other disorders associated with PVL include neonatal sepsis, NEC, and other inflammatory processes [58]. Neuroimaging studies indicate that PLV in its various forms occurs in 40% of EP-born children [59].

Growth and metabolic bone disease

Preterm birth, in particular EP/ELBW birth, has implications for postnatal nutrition and growth. In this setting, the mechanical function of the gastrointestinal tract is not fully developed, and acute illness can disrupt adequate nutrient provision [60]. Several nutrition strategies for VP- and EP-born infants have been developed. However, optimal nutrient amounts and composition are still under investigation [61]. Moreover, proper growth velocity and the definition of extrauterine growth restriction in infants born preterm are still under debate [62,63].

At term equivalent age, preterm neonates are lighter and shorter with a smaller head circumference than neonates born at term with appropriate BW [64]. Infants born preterm have also been found to have a different body composition at term equivalent age compared to TB infants, including markedly lower fat-free mass and a higher percentage of total body fat [64]. Poor postnatal growth has been associated with poor long-term neurological outcomes [65].

Preterm birth occurs during a critical period of bone mineralization. Nearly 80% of fetal calcium and phosphorus accumulates in the third trimester and EP- and VP-born neonates are therefore deprived of the positive skeletal events that normally occur during this stage of intrauterine development. Poor skeletal mineralization has been found in 30% of VLBW infants and in more than 50% of those weighing less than 1,000 g at birth [66]. Placental insufficiency and postnatal exposure to other factors such as inadequate postnatal intake of vitamin D, calcium, and phosphorus, extended periods of total parenteral nutrition, immobilisation, and treatment with diuretics and steroids may impede normal bone mineralisation [67-70]. Neonatal metabolic bone disease or osteopenia of prematurity are terms used to describe a state of reduced bone mineral content (BMC) in preterm infants. Depending on the severity of demineralisation, osteopenia can remain clinically silent, develop as rickets, or lead to fractures of long bones or ribs [68].

Treatment in the neonatal intensive care unit

Modern NICUs were first established in 1950–70 with the setting up of special care units for infants and use of incubators providing oxygen supply and preserving heat

and humidity. From the 1960s, the development of mechanical ventilators and continuous positive airway pressure (CPAP) has led to reduced mortality among infants with RDS [71].

In 1972, a randomised controlled trial demonstrated that antenatal corticosteroids administered at least 24 hours before delivery to pregnant mothers admitted with threatening premature delivery reduced the incidence of RDS in preterm-born neonates [72]. During the 1980s, antenatal corticosteroids were widely used, reducing the incidence and severity of the two leading causes of neonatal mortality and morbidity: neonatal RDS and intracranial haemorrhage [73]. A single course, and a repeat course if indicated, of antenatal corticosteroids is now considered routine treatment when preterm delivery before 34 weeks' gestation is anticipated [73].

Surfactant replacement therapy, first described in 1980, aids immature airspace in overcoming high surface tension and supports alveolar inflation and expansion when alveoli are filled with air [74]. Surfactant has been widely used since the 1990s to either prevent or treat RDS, and has been shown to reduce mortality, although not the incidence of chronic lung disease [35,75].

During the 1990s and 2000s, lung-protective strategies for respiratory support including volume-targeted ventilation [71], early CPAP [76], and less invasive surfactant administration [77], were initiated and have been shown to reduce the need and duration of mechanical ventilation. The most recent measures to improve the outcome of preterm neonates include prenatal magnesium sulphate infusion for fetal neuroprotection [78] and delayed cord clamping for reduced risk of hospital mortality, NEC, and intracranial haemorrhage [79]. Caffeine, a respiratory stimulant, has been used for more than 30 years to reduce the frequency of apnoea of prematurity. In 2006, a randomized trial of caffeine therapy for apnoea of prematurity showed that caffeine improved the rate of survival without neurodevelopmental disability (NDD) at 18–21 months in infants with VLBW [80].

Therapy and supportive care for EP/ELBW-born neonates are continuously improving to minimise injury and preserve growth. Over the years, there has been a shift in several

paradigms. In the early years of neonatology, oxygen supplementation was the sole therapeutic option for respiratory distress. In 1951, retrolental fibroplasia (or retinopathy of prematurity (ROP)) was described after exposure to high oxygen therapy [81], and restricted oxygen therapy was hence adapted [71]. Initially, infant formulas were preferred, whereas breast milk was considered nutritionally inadequate for preterm infants and also presented with storage and usage problems [82]. This practice has since changed, and breast milk is now considered a vital source of nutrients and a multitude of bioactive substances [83]. Skin-to-skin or *kangaroo care* out of the incubator is another example of handling of the neonates that was considered potentially dangerous and therefore restricted to limited duration only for those considered clinically stable. Today, *kangaroo care* is considered well tolerated with a number of biological benefits for the neonate [84]. Also, the use of postnatal corticosteroids has changed. Although they were initially reported to have positive effects on respiratory mechanics and facilitating weaning from mechanical ventilation, higher incidence rates of NEC, growth deficiency, and poor neurodevelopmental outcomes in neonates treated with postnatal corticosteroids were subsequently observed [85]. Postnatal corticosteroids are currently considered as a rescue treatment limited only to subjects with severe respiratory failure who require substantial ventilatory support and a high fraction of supplementary oxygen [86].

In the contemporary NICU, the principle of *the golden hour* has been adapted from adult trauma management. This includes implementing all evidence-based interventions within the initial 60 minutes after birth [87]. Current evidence supports the application of *the golden hour* concept by showing a reduced incidence of hypothermia, ROP, BPD and intraventricular haemorrhage in VLBW/ELBW neonates [88].

In future, stem cell treatment shows promise in the prevention of preterm lung and neurological complications [89,90], with umbilical cord blood as a new and convenient source of stem cells. Hopefully, this intervention could represent a new era in neonatal medicine.

2.2 Long-term outcomes of preterm birth

There has been increasing interest in understanding the long-term effects of premature birth. Several studies have found prematurity to be a risk factor for motor impairment [91], cerebral palsy (CP) [92], vision and hearing defects [93], epilepsy [94], impaired cognitive function [95], psychiatric disorders [8], behavioural problems and learning disabilities [96-98]. Prematurely born subjects are also at increased risk of diseases such as asthma [99], obstructive lung disease [100], cardiovascular disease [4-6], metabolic syndrome [7], and osteoporosis [101,102], as well as and shorter life expectancy [9]. Overall, the risk of unfortunate long-term outcomes increases with decreasing GA at birth [103].

Preterm-born individuals have been found to have lower quality of life. Although the impact of low BW and decreasing GA is greatest during the younger years, this also extends into adolescence and adulthood [104,105]. Compared to their TB counterparts, individuals born preterm also have difficulties in social functioning and tend to achieve lower educational levels, have lower incomes, and fewer children, and less likelihood of getting married or living in cohabitation [106].

2.2.1 Respiratory outcomes

Long-term follow-up studies of EP-born infants with BPD have reported abnormal lung function with variable degrees of airway obstruction, bronchial hyperresponsiveness to direct stimuli or exercise, pulmonary hyperinflation, and impaired gas diffusion capacity [100]. Recurrent wheeze is common in infancy and early childhood, and about half of EP-born children are admitted to hospital in the first year of life due to respiratory tract infections [107]. This increased risk of hospitalisation persists into adulthood [108] along with a higher prevalence of cough, wheeze, and asthma-like symptoms in [109]. Children and adolescents born preterm have reduced lung function, especially those with a history of BPD [110]. This observation raises concerns about the susceptibility of BPD survivors to developing a chronic obstructive pulmonary disease phenotype with ageing [111].

2.2.2 Cardiovascular outcomes

Epidemiological studies have identified preterm birth as an independent risk factor for subsequent cardiovascular disease, including hypertension [6], ischaemic heart disease [5], stroke [112], and early heart failure [4]. It has been suggested that the preterm heart represents a unique form of cardiomyopathy. This is characterised by a reduced myocardial functional reserve [113], and unique geometric and functional cardiac changes at rest, the severity of which seems to be correlated to the degree of prematurity [41,114]. Mild cardiac dysfunction, high blood pressure and vascular endothelial dysfunction are detectable in young adulthood [115,116]. Therefore, a detailed birth history is important so appropriate follow-up can be arranged.

2.2.3 Neurodevelopmental outcomes

The term 'neurodevelopmental outcomes' typically refers to neurological, intellectual, and/or sensory outcomes. The main neonatal comorbid conditions that may influence later neurodevelopmental outcomes in subjects born preterm are brain pathology, chronic lung disease, NEC, sepsis, and ROP [117]. Overall, neurodevelopmental outcomes in preterm children have improved over the last decades, except in those infants born at GA of 22–24 weeks [118].

Motor problems

Motor impairment is one of the most common neurodevelopmental disorders in preterm-born children [91], ranging from mild motor coordination deficits to severe CP [119]. Data from the collaborative network *Surveillance of Cerebral Palsy in Europe* reported a decline in rates of CP from 60.6 per 1000 VLBW infants in 1980 to 39.5 per 1000 VLBW infants in 1996 [120]. For comparison, the prevalence of CP in Norwegian children born during 1996–2009 was 2.1 per 1000 live births [121]. Concomitant with increased survival rates among ELBW-born children in the early 1990s, an increase in the prevalence of CP was also reported. However, after the turn of the millennium, the rate of CP among children born ELBW declined from 13% during the 1990s to 5% in 2000–02 [122].

Motor deficits in coordination, balance, gross- and fine motor control, and visual-motor integration, have been reported in preterm-born children without CP [123]. The term

'developmental coordination disorder' (DCD), defined as a marked impairment in the development of motor coordination that is not explained by a known physical disorder and is not due to an intellectual impairment, may be applied if the motor disorder interferes with activities of daily living or academic achievement [124,125]. In unselected schoolchildren, the prevalence of DCD is about 5–8% [125]. Among schoolchildren born VP/VLBW in the late 1970s to 2007, the prevalence of motor coordination disorder has been reported to be in the range of 8–37% [126], with similar reported prevalence also in young adulthood [127]. There are indications of a slight decrease in the prevalence of motor coordination difficulties among children born VP/VLBW after 1990 [128]. The prevalence of CP and motor coordination difficulties in a Norwegian follow-up study of subjects born EP/ELBW in 1999–2000, on which this thesis is based, was 11% and 17%, respectively [129].

Sensory impairments

Preterm children are at increased risk of sensory impairments including hearing loss and visual impairment ranging from squint/refractive errors to total blindness. The prevalence of deafness and blindness among EP/ELBW-born children in the Norwegian follow-up study on which this thesis is based was 1% and 2%, respectively [129].

Intellectual deficits

Intellectual functioning comprises general mental ability including reasoning, planning, problems-solving, and abstract thinking. Intellectual disability is a generalised neurodevelopmental disorder characterised by impaired adaptive functioning and an intellectual deficit confirmed by standardised measurement of intelligence, with an intelligence quotient (IQ) score that is two standard deviations (SDs) below the mean 100 in the general population (i.e. IQ score below 70) [130,131].

A gradient relationship has been observed between BW and IQ [132]. A meta-analysis of 71 studies including 7752 children born EP/VP and 5155 controls demonstrated a large difference (0.86 SD, or approximately 13 points in IQ) in intelligence between EP/VP-born children and their full-term peers. This difference was stable over age (5-20 years) and birth year (1990-2008) [95].

Mental health problems

Preterm-born children, adolescents and adults have an increased risk of symptoms related to anxiety, inattention, and social and communication problems, which manifest in a significantly higher prevalence of emotional disorders, attention-deficit/hyperactivity disorder, and autism in the preterm-born population [133,134]. Studies have reported a 3 to 4-fold increased risk of psychiatric disorders in the preterm-born population, compared to the TB group [133,135]. A study of children aged 11 year who were born at GA of <26 weeks found these children to be three times more likely to have a psychiatric disorder than TB classmates (23% vs. 9%), including 4-fold higher risk of attention-deficit/hyperactivity disorder (11.5% vs. 2.9%) and almost 5-fold higher risk of emotional disorders (9.0% vs. 2.1%) [136].

Growth and body composition

Preterm birth influences later growth and body composition beyond infancy. Studies have consistently reported that EP/ELBW-born subjects attain lower growth parameters than TB controls throughout childhood and adolescence, although studies disagree on the severity of impact on growth and when catch-up growth occurs [137-139]. Among VLBW-born subjects, those born small for gestational age (SGA) and males seem to have poorer growth outcome than those with BW appropriate for GA (AGA) and females [140,141].

Whether the body composition in preterm-born subjects differs from that in TB peers remains unclear. Some report that EP-born and TB children have similar body composition, whereas others have found a relative lack of lean mass (a measure of skeletal muscle mass) and lower total body fat in EP-born boys [139,142,143]. Adults born ELBW have been found to have a higher percentage of body fat and lower lean mass than TB adults [144]. Increased visceral fat distribution has been described for both preterm-born children and adults [145,146].

The hypothesis of the developmental origins of adult disease postulates that prenatal and early life environment may result in permanent changes in metabolism with subsequent increased risk of disease such as cardiovascular disease and type 2 diabetes in adulthood [147]. The mechanisms leading to abnormal metabolic homeostasis are

complex and remain unclear, however, intrauterine as well as postnatal growth seems to play a role [148]. Body composition is influenced by antenatal factors and early growth, and may play a role in this metabolic shaping by being a mediator in the process [148]. Evaluating body composition in future generations of EP/ELBW-born children is therefore of particular relevance in terms of cardiometabolic risk assessment.

Bone mass

Bone mass increases throughout childhood and adolescence until peak bone mass is achieved at around the age of 30 years. Hereafter, bone mass gradually decreases with age [149]. Peak bone mass is determined by a number of factors, including genetics, ethnicity, sex, timing of puberty, skeletal muscle mass, physical activity, calcium intake, and vitamin D supplementation [149]. A reduced peak bone mass is an important determinant of osteoporosis and fractures in later adulthood. The gold standard in estimating bone mass and establishing the diagnosis of osteoporosis is measurement of bone mineral density (BMD) by using dual-energy X-ray absorptiometry (DXA) [150].

The potential effect of prematurity on BMD later in life is not fully understood. Preterm infants have lower BMD than TB peers in their first year of life [151] while some studies have found the BMD deficit persisting into prepubertal age [139,152,153] and adulthood [101,102,154]. On the other hand, other studies reported that preterm-born children [155,156] and adults [157] have similar BMD as their TB counterparts. A reduced BMD implies an increased risk of developing osteoporosis. Further follow-up studies across generations and preterm birth-cohorts are warranted given the major public health problem of fractures associated with osteoporosis [158].

3. INTRODUCTION TO PHYSICAL ACTIVITY

PA is considered an important mediator of health and disease and the promotion of adequate PA has become an important part of the public health agenda [10,11,159]. Worldwide, physical inactivity is estimated to cause 9% of early mortality or more than 5.3 million deaths per year [10]. A number of epidemiological studies have demonstrated a dose-dependent relationship between PA and the risk of highly prevalent non-communicable diseases such as type 2 diabetes, metabolic syndrome, hypertension, coronary heart disease, obesity, stroke, cancer, and musculoskeletal disorders [10,11]. Low cardiorespiratory fitness is also an independent predictor of cardiometabolic disease and all-cause mortality [160].

Epidemiological studies have found that individuals born VP/VLBW or EP/ELBW are less physically active than TB peers [12-17], although the findings are not consistent [161-163]. Further research investigating PA participation and exercise capacity in this population would prove valuable in guiding adequate follow-up and appropriate intervention.

3.1 Definitions

Physical activity is defined as *'any bodily movement produced by skeletal muscles that require energy expenditure'* [164]. PA can be classified as either structured or incidental [165]. Incidental PA is not planned and usually is the result of daily activities at work, at home, or from transportation, e.g. walking or cycling. **Exercise** is structured PA that is planned, repetitive, and purposeful, undertaken to promote health and skill-related fitness [164]. There are four dimensions of PA: mode, frequency, duration, and intensity.

Exercise capacity is the ability of an individual to increase their oxygen consumption above their oxygen consumption at rest, or in other words, the ability to perform strenuous exercise over a time period [166]. An individual's capability of performing persistent PA or exercise has no standard definition, and the terms 'exercise capacity', 'cardiorespiratory endurance', 'cardiovascular endurance', 'aerobic exercise capacity', or 'cardiorespiratory fitness' are all used.

In this thesis, the term ‘maximal exercise capacity’ is used to define the maximal amount of physical exertion a person can sustain and is expressed as the maximal or peak oxygen consumption (VO_2) and completed distance, measured using the maximal treadmill exercise test. For the purpose of this thesis, the term ‘physical activity’ encompasses both participation and performance (including endurance, intensity, and proficiency) in PA.

3.2 Physical activity in childhood and adolescence

PA is an important part of childhood. It is associated with improved physical skills [167] and exercise capacity [168] as well as with many psychological and social health benefits such as fewer mental health problems, improved self-esteem, and social interaction [169-171]. The social aspect of sport participation is important, as team sports have been associated with further improved health outcomes compared to individual sports [169].

3.3 Recommendations for physical activity

There is general consensus on health benefits from regular PA in all age groups. The World Health Organization recently published new guidelines on PA and sedentary behaviour, providing evidence-based public health recommendations on the intensity and types of PA that offer significant health benefits while mitigating health risks [172]. These guidelines address different age groups (children, adolescents, adults, and older adults) and include specific recommendations for people living with disabilities and chronic conditions. Children and adolescents are recommended to engage in moderate-to-vigorous intensity PA for an average of 60 minutes per day. Adults are recommended to undertake 150–300 minutes of moderate-intensity PA, or 75–150 minutes of vigorous-intensity PA, or other equivalent combinations, per week. On a rating scale of perceived exertion ranging from 0 to 10 relative to an individual’s personal capacity, moderate-intensity PA is rated 5–6 and vigorous-intensity PA is rated 7–8 [172].

3.3.1 Determinants of physical activity behaviours

Several factors influence PA behaviours. Overall, male sex and high socio-economic status are associated with higher levels of PA [173,174]. In children, perceived physical competence, parental support, access to sports programmes or facilities, opportunities to be active, and time outdoors are positively correlated with increased PA levels [174]. Population subgroups at risk of physical inactivity include girls, older adolescents, and those from minority ethnic groups [174]. In school-aged children, PA levels are highest in early school age and gradually decline over time, especially during adolescence [175].

Health status is an important determinant for participation in PA. Children with chronic disease or physical or intellectual disabilities are less physically active compared to healthy peers [176]. Poor motor proficiency has been demonstrated to be associated with a reduced PA levels and persistently lower cardiorespiratory fitness [177,178]. It is possible that children with poor motor skills are more likely to choose a more sedentary lifestyle as a way to avoid their movement difficulties [179].

PA behaviour tracks over the lifespan [180]. A study from Finland has demonstrated that a physically active lifestyle starts to develop early in childhood and PA behaviour remains moderately to highly stable during the life course from youth to adulthood [181]. This suggests that successful early-life interventions to increase PA may improve health throughout the life span [180].

3.4 Exercise capacity and peak oxygen consumption

Maximal exercise capacity is the maximal amount of physical exertion a person can sustain. Maximal exercise capacity can be determined objectively by measuring the physiological variable *maximal oxygen consumption*; which is the maximal amount of oxygen that can be consumed by the body per unit of time [182]. VO_2 rise with increasing workload and reaches a plateau (maximal VO_2). Of note, VO_2 plateauing does not always occur, particularly in children, and the highest VO_2 observed at the point of maximal exhaustion during an exercise test is reported as the peak VO_2 [183]. Peak VO_2 is measured in litres per minute, which indicates the volume of oxygen consumed per minute, and in millilitres per kilogram per minute, which indicates the potential to

move the body during physical exertion performed over time. Low exercise capacity is associated with an increased risk of cardiovascular disease, and higher rates of mortality attributable to various cancers, and all-cause mortality [184]. The American Heart Association has recommended that cardiorespiratory fitness, quantified as maximal VO_2, should be used as a clinical vital sign and be assessed regularly [184].

3.4.1 Determining factors of maximal oxygen consumption

Exercise capacity is influenced by several factors including PA, body size and composition, genetics, sex, and age [185,186]. There are individual variations in training responsiveness and it has been estimated that 50% of peak VO_2 is inherited [186]. From childhood and onwards, males have a higher peak VO_2 than females due to a higher haemoglobin concentration, more muscle mass, lower fat mass, a larger cardiac stroke volume, and probably because of a higher level of PA [187,188]. Several equations for reference values for peak VO_2 according to age and sex have been developed [189]. In adults, peak VO_2 decline by approximately 6–8% every decade after the age of 30 years [189,190].

3.4.2 Cardiopulmonary exercise testing in the laboratory

Cardiopulmonary exercise testing (CPET) is a comprehensive non-invasive method for assessing the exercise responses of the pulmonary, cardiovascular, haematopoietic, and skeletal muscle system, and measures peak or maximal VO_2 when performed until maximal exertion [191]. In clinical settings, CPET is used to evaluate the degree of exercise intolerance, prognosis and effects of therapeutic interventions in many diseases including cystic fibrosis, and chronic heart and lung diseases [191] .

CPET is usually performed in a clinical laboratory with use of a stationary cycle ergometer or treadmill, whereby exercise intensity is progressively increased according to standardised protocols. During the test, the test subject breathes through an airflow- or volume-transducing device that measures inspiratory and expiratory volumes as well as minute ventilation. A two-way valve enables sampling of expired air, and a gas analyser measures the oxygen and carbon dioxide (CO_2) concentrations. The corresponding expired volume is then used to calculate VO_2 and CO_2 production. Heart

rate (HR) is usually measured from the R-R interval obtained on an electrocardiogram, and a pulse oximeter provides estimates of arterial oxygen saturation [191].

The Fick principle states that maximal VO_2 equals the cardiac output multiplied by the difference in arterial and venous oxygen content [192]. From this, we can infer that oxygen consumption is influenced by ventilation, gas exchange in the alveoli, arterial oxygen saturation, central and peripheral blood flow, and active muscle metabolism. In the general population, peak VO_2 is mainly limited by cardiovascular function and not due to lung capacity [182].

3.4.3 Cardiopulmonary exercise testing with concomitant laryngoscopy

The method of combining CPET with continuous laryngoscopy during exercise (CLE) was developed by a research group today known as the Bergen ILO group, who first described the technique in 2006 [193]. The CLE test requires flexible video-laryngoscopy to be performed during maximal CPET. While allowing concomitant visual assessment of the larynx, it also provides information on gas exchange, and cardiovascular and respiratory capacities. The CLE test is the gold standard for diagnosing exercise-induced laryngeal obstruction, which is a common cause of exercise-related breathing problems [194,195]. Diagnosis is based on visual observation of inappropriate, transient, and reversible narrowing of the larynx during exercise [194].

Peak VO_2 measurements based on standard CPET, are highly reproducible [191]. Additional equipment involved in setting up combined CPET with CLE results in extra weight, and can possibly introduce air leaks, as well as be a source of stress for patients, all of which may influence performance and gas exchange. One study found no systematic difference in gas exchange parameters when using bicycle CPET performed either with or without continuous laryngoscopy [196]. However, further studies are warranted to establish whether parameters of gas exchange obtained by maximal treadmill CPET with or without CLE setup can be used interchangeably by determining agreement between measurements using the two methods. A reliability study was therefore conducted as part of this thesis, which will be described later [197].

3.5 Preterm-born subjects and physical activity

Preterm-born individuals may carry a range of characteristics that can influence their participation in PA and their exercise capacity. This includes increased respiratory symptoms, reduced lung function, reduced muscle mass and strength, poor motor skills, and poor visual activity, which may discourage individuals from undertaking PA [167,198-200]. Furthermore, low self-confidence and perceived physical ability, as well as inattention and hyperactivity, all represent barriers to PA [167,201]. Parents of preterm-born children may perceive their child as highly vulnerable and thus could adopt overprotective parenting practices that, in turn, may influence these children's participation in PA [202].

The question of whether preterm-born subjects are less physically active than their peers is not fully resolved. Lower levels of PA in children and young adults born VP/VLBW or EP/ELBW are shown by self-reports in several studies [12-17]; however, others have reported no difference when compared to TB control groups [161-163] (Tables 2, 3, and 4, pp. 97–9). A few studies were conducted using objective measures to assess PA. Using accelerometers, three studies found no differences in PA between children born VP/VLBW or EP/ELBW and TB controls at ages 10–15 years [203-205]. Another recently published study of children aged 6–7 year found that EP-born boys, on average, spent 25 minutes less in moderate-to-vigorous PA per day and had more sedentary time, compared to TB controls [206]. Likewise, in studies comparing adults, some have found ELBW- or VLBW-born subjects and their TB counterparts to be equally physically active [207,208] whereas another study found adults born VLBW to be less physically active than their TB controls [209]. The Helsinki Study of Very Low Birth Weight Adults measured PA using accelerometers and observed similar PA levels in both adults born VLBW and controls, despite self-reporting of up to 50% less PA in the preterm group [12,208]. Heterogeneity of the studies may be explained by different methods used for PA assessment, inclusion of different populations of preterm-born individuals, age differences at the time of assessment, and differences in neonatal care. Thus, it is still not clear whether individuals born preterm are less physically active than TB peers [199].

3.6 Preterm-born subjects and exercise capacity

There are a limited number of studies assessing the exercise capacity of children and adults born preterm (Tables 5 and 6, pp. 100–04). As in the case of studies investigating PA levels, different research groups report inconsistent results.

A graded relationship between low GA and reduced fitness, as determined by cycle ergometry, has been described among Swedish male conscripts [210]. In a systematic review and meta-analysis on the effect of premature birth on exercise capacity, preterm-born individuals had approximately 13% lower peak VO_2 than TB control subjects. However, the majority of the 22 included studies did not show a significant difference between preterm-born and TB participants [211].

Several explanations for the deficit in exercise capacity observed in preterm-born individuals have been proposed, including low levels of PA, reduced lean body mass, and poor growth and development [14,204,212]. Impaired myocardial functional reserve has recently been shown to underlie peak VO_2 reduction in young preterm-born adults [213]. Motor coordination difficulties is a predictor of exercise capacity in ELBW-born children, as demonstrated by Burns *et al.* [214]. It has been suggested that children with motor difficulties experience earlier fatigue due to higher oxygen utilisation than well-coordinated individuals at submaximal workload [215].

Reduced exercise capacity in preterm-born children may be secondary to underlying neonatal lung injury. A recent study found 14% lower peak VO_2 in EP-born subjects with moderate/severe BPD, compared to TB controls [216]. In agreement with other studies [14,15], no significant relationship between lung function (forced expiratory volume in 1 second (FEV_1)) and peak VO_2 was observed. Expiratory flow limitation and an exaggerated ventilatory response have also been found to contributed to respiratory limitation to exercise in EP-born children [216]. By contrast, other studies found no differences in peak VO_2 when comparing preterm-born subjects with BPD to TB controls [217,218].

Upper airway pathology may play a role in preterm-born individuals' exercise capacity. In those with a paralysed left vocal cord, the paramedian position of the left vocal cord can potentially compromise airflow and exercise capacity. Røksund *et al.* found that of

11 EP/ELBW-born adults with a history of neonatal PDA surgery, seven had LVCP [219]. Despite laryngeal narrowing induced by LVCP and associated collapse of left supraglottic structures during exercise, peak VO_2 did not differ between subjects with and those without LVCP. Further evidence is needed to better understand long-term consequences of laryngeal pathology in EP/ELBW-born adults [220].

3.7 Gaps in current knowledge

So far, much knowledge has been gained on health prospects in survivors of EP/ELBW birth. However, their outcomes across their life span have only been partly explored. As the first generations of EP/ELBW-born cohorts enter adulthood, there is an increasing awareness that non-communicable diseases in this population will have a growing clinical and public health importance. Some advocate that preterm birth should be recognised as a chronic condition that requires long-term follow up [221].

It is well established that regular PA is associated with many health benefits [10,11]. Therefore, it follows that PA would be particularly important in the EP/ELBW-born population, given their susceptibility to later chronic diseases. However, there are still knowledge gaps in terms of PA behaviour and exercise capacity in the preterm-born population. Identification of predictors of physical inactivity and reduced physical fitness will be important to help promote and facilitate participation in PA. Therefore, PA behaviour and exercise capacity need to be further explored as new generations of EP/ELBW-born children grow up.

Date of completed literature study: 10.10.21

4. STUDY AIMS AND RESEACH QUESTIONS

The overall aim of the work presented in this thesis was to investigate long-term outcomes in survivors of EP/ELBW birth, with a focus on PA and exercise capacity. The specific aims and research questions (RQs) were the following:

Aim 1 (Paper I-III): To investigate PA in EP/ELBW-born children and young adults.

- **RQ1:** Do EP/ELBW-born children and young adults participate and perform differently in PA compared to TB controls, and is NDD associated with poorer PA-related outcomes?

Aim 2 (Paper I): To investigate body composition in EP/ELBW-born children.

- **RQ2:** Do EP/ELBW-born children differ from TB controls with respect to body composition, and is the association between PA frequency and body composition different in EP/ELBW-born children compared to TB controls?

Aim 3 (Paper II): To investigate whether pre-school motor coordination problems, behavioural problems, and borderline intellectual functioning are associated with PA at school age in healthy EP/ELBW-born children.

- **RQ3:** Are motor coordination problems, behavioural problems, and borderline intellectual functioning in healthy EP/ELBW-born children aged 5 years associated with participation and performance in PA at age 11 years?

Aim 4 (Paper III): (1) To investigate the prevalence of LVCP in young adults with a history of EP/ELBW birth and PDA surgery, (2) to investigate consequences of LVCP.

- **RQ4:** (1) What is the prevalence of LVCP among EP/ELBW-born adults who underwent neonatal surgical PDA closure? (2) Is LVCP associated with abnormal voice and breathing, reduced lung function and exercise capacity, or laryngeal obstruction during exercise?

Aim 5 (Paper III): To investigate lung function and exercise capacity in young adults with a history of EP/ELBW birth and PDA surgery.

- **RQ5**: Do EP/ELBW-born adults who underwent neonatal surgical PDA closure have reduced lung function or exercise capacity compared to: (1) EP/ELBW-born adults not exposed to PDA surgery and (2) TB controls?

The group of young EP/ELBW-born adults who underwent PDA surgery was assessed by CPET with continuous laryngoscopy (the CLE test) (Paper III), whereas the EP/ELBW-born group not previously exposed to PDA surgery, as well as TB controls, were assessed by standard CPET. For comparison of CLE data to standard CPET data (RQ5), it was necessary to determine the agreement of gas exchange parameters between these two methods.

Aim 6 (Paper IV): To investigate the reliability of gas exchange parameters, including peak VO_2, by comparing CLE data and standard CPET data.

- **RQ6:** Can measurements of gas exchange parameters, including peak VO_2, obtained from a CLE test be used interchangeably with those obtained from standard CPET?

5. ETHICS

The studies presented in this thesis were approved by the Regional Committee for Medical Health Research of Western Norway (reference number 2003/20.04, 2009/2271, 2014/601, 2017/1174 and 2017/628). Informed written consent was obtained from all participating subjects or, if aged under 16 years or not competent to give consent, from their parent. The studies were planned and performed in accordance to the Declaration of Helsinki [222] and the Norwegian Health Research Act [223].

The studies presented here relied on questionnaire surveys and non-invasive clinical examinations and tests. Hence, there were low risk, with minimal inconveniences to participants and their guardians. Radiation exposure in whole-body DXA scan is considered to be low and comparable to the equivalent of 1 day of background radiation exposure at sea level [224]. Further, children in the studies presented here were offered dermal application of a local anaesthetic (Emla®) prior to blood sample collections to minimise pain.

6. SUBJECTS AND METHODS

6.1 Design and study population

6.1.1 Design

The work presented in this thesis was based on observational studies. Studies reported in Papers I, II and III were designed as prospective population-based cohort studies. The study presented in Paper IV had a randomised crossover design.

6.1.2 EP/ELBW-born subjects (Papers I, II and III)

Subjects described in Papers I, II and III participated in a prospective population-based cohort study, including all survivors of EP birth (GA <28 weeks) or those born with ELBW (<1000 g) in Norway during the period 1999–2000 [3]. All obstetric and paediatric departments in Norway took part in recruitment. The children have been invited to participate in follow-up studies at age 5, 11, and 19 years.

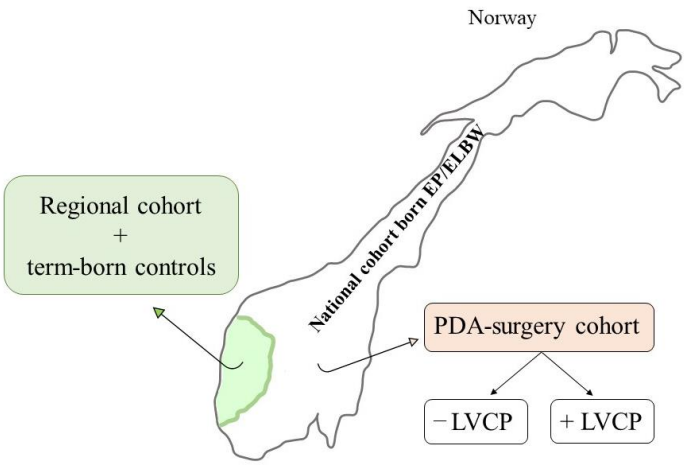

Figure 3 Overview of the study population and subgroups.
EP, extremely preterm; ELBW, extremely low birth weight; LVCP, left vocal cord paralysis; PDA, patent ductus arteriosus.

In addition, two subsamples from the overall *national cohort* are defined as follow (Figure 3):

- The EP/ELBW-born *regional cohort* included a sub-sample of individuals whose mothers were living within the area served by the Western Norwegian Health Authority, i.e. the counties of Sogn og Fjordane, Hordaland, and Rogaland.

- The *PDA-surgery cohort* included all EP/ELBW-born individuals from the nationwide cohort who had undergone neonatal open PDA surgery. This group was further subdivided into those with and those without LVCP.

6.1.3 Term-born controls (Papers I, II and III)

TB children were recruited as controls to the regional EP/ELBW-born cohort at the time of the follow-up visit at age 11 years. TB children were identified using birth protocols from the maternity ward. Each EP/ELBW-born child was matched with the next-born child with similar sex, GA >37 weeks, and BW >3000 grams (Norwegian 10-centile for BW [20]). Invitation to participate was by postal letters addressed to the TB children's parents. If consent was not provided, the next TB child delivered closest in time to the index-subject was approached for inclusion until an appropriate and consenting match was found.

6.1.4 Healthy youths and adults (Paper IV)

Healthy volunteers aged 15–35 years who were actively engaged in endurance training at least four times a week were recruited among colleagues and students living in Bergen. Subjects who reported breathing difficulties at rest or during exercise, or who had any medical issues except well-controlled asthma were not enrolled.

6.2 Data collection: Papers I, II and III

Data were collected during the participants' stay in NICU and later at three occasions:

1) At age 5 years, data were collected from the complete national cohort on questionnaires completed by the participants' parents including information on health issues such as behavioural problems and medications used. Neurosensory, cognitive, and motor functions were assessed by paediatricians, physiotherapists, and psychologists working at the local hospitals (n = 19) who were responsible for the follow-up of each individual participant (Paper II).

2) At age 11 years, data were collected from the complete national cohort by use of questionnaires completed by the participants' parents, that addressed health, medications, and PA. The regional cohort and TB controls underwent clinical examinations including DXA scanning at Haukeland University Hospital or Stavanger University Hospital (Papers I and II).

3) At age 19 years, the PDA-surgery cohort, the EP/ELBW-born regional cohort, and TB controls completed questionnaires addressing health issues, including participation in PA. They also underwent lung function tests and CPET at Haukeland University Hospital or Stavanger University Hospital (Paper III).

6.2.1 Perinatal characteristics and definitions used (Papers I, II and III)

The extent of routine examination during NICU stay was left to the discretion of each unit. The obstetricians and paediatricians caring for the EP/ELBW-born children at the NICU completed questionnaires on neonatal and perinatal characteristics. These data were merged with data from the Medical Birth Registry collected through compulsory notifications, providing information on maternal health, pregnancy, and delivery. The Medical Birth Registry also provided information on all stillbirths and live births during the study period, thus providing the total number of eligible children within the defined BW and GA limits.

In this study, *BPD* was defined as still dependent on oxygen supplementation and/or assisted ventilation at GA of 36 weeks [34] and *SGA* was defined as BW below the 10th percentile according to Norwegian growth references [20].

GA was primarily determined by routine ultrasonography at 17–18 post-menstrual weeks. If results from the ultrasound scan were unavailable, GA was determined using the date of the mother's last menstrual period. *PDA* was diagnosed at the discretion of the participating NICUs based on echocardiographic assessment (left atrium to aortic root ratio >1.5) and clinical signs (cardiac murmur, bounding hyperdynamic pulses and signs of cardiac or respiratory insufficiency) [45]. Treatment options for PDA included a conservative approach (watchful waiting, fluid restriction and respiratory support), pharmacological treatment with indomethacin, or open surgical closure performed by suture ligation or clip application. PDA surgery was conducted at four different regional hospitals.

6.2.2 Assessments at age 5 years (Paper II)

In 2004-05, the parents of EP/ELBW-born children from the national cohort responded to questionnaires and the children were examined at 19 local paediatric departments by paediatricians, physiotherapists, and psychologists. In the study described in Paper II, the information obtained was used to classify the participants as either *healthy* or with *NDD.* Abnormal results obtained on motor function, behavioural problems, and intellectual functioning were considered possible predictors of different aspects of PA at age 11 years.

Cerebral Palsy: Gross Motor Function Classification System

Paediatricians classified the EP/ELBW-born children with CP according to the Gross Motor Function Classification System (GMFCS) [225]. This five-level classification system describes the gross motor function in children and youths with CP according to functional abilities, the need for assistive technology including mobility devices, and quality of movement. Level I indicates walking abilities without restrictions whereas level V indicates very limited mobility abilities, even with use of assistive technology.

Motor coordination problems: the Movement Assessment Battery for Children

Physiotherapists assessed the EP/ELBW-born children's motor function by using the Movement Assessment Battery for Children (MABC) [226] [226]. The MABC consists of eight tasks assessing balance (static and dynamic), ball skills, and manual dexterity (Table 7). Age-specific total motor impairment scores range from 0 to 40, increasing with poorer motor function. The total score is interpreted using normative tables. A total score below the 5th percentile (MABC5) is defined as abnormal by the MABC manual and indicates motor coordination problems [226,227]. The MABC has different age bands. For the study presented in Paper II, age band I (4–6 years) was used.

Intellectual functioning: Wechsler Preschool and Primary Scale of Intelligence-revised

Psychologists examined the EP/ELBW-born children's intellectual function by using the Wechsler Preschool and Primary Scale of Intelligence-revised (WPPSI-R). The test was developed for children aged from 2 years and 3 months to 7 years and 3 months. The WPPSI-R provides sub-tests for verbal IQ and performance IQ. A full-scale intelligence quotient (FIQ) score is calculated from the sub-scores and represents the child's general intellectual ability [131]. The reference mean value for the FIQ score is 100 with an SD of 15. In the study presented in Paper II, borderline intellectual functioning was defined as an FIQ of 70–84 points (FIQ70–84).

Table 7 The Movement Assessment Battery for Children (MABC)

Subtests	**Items**	**Score (points)**
Manual dexterity	• Posting coins (both hands tested) • Threading beads • Bicycle trial	0–15
Ball skills	• Catching bean bag • Rolling ball into goal	0–10
Balance (static and dynamic)	• One-leg balance (both legs tested) • Jumping over cord • Walking heels raised	0–15
Total MABC score (sum of sub-test scores)		**0–40**

Behavioural problems: the Strengths and Difficulties Questionnaire

Participants' parents completed the Strengths and Difficulties Questionnaire (SDQ). The SDQ is a general behavioural screening questionnaire for 4 to 17-year-old children. It consists of five subscales: emotional problems, hyperactivity/inattention, conduct problems, peer problems, and prosocial behaviour. Five items per subscales are scored on a three-point scale: 'not true' (0), 'somewhat true' (1), and 'certainly true' (2). A *Total Difficulties Score* (TDS), ranging from 0 to 40, is computed by adding the first four subscale scores (except the score for prosocial behaviour). A TDS ≥90th percentile (TDS90) was considered an indicator of risk of having a mental health problem [228]. The reference group for normal SDQ score comprised children from Oppland County, Norway, born in 2001, attending the public health care routine programme for children [229]. In the study presented in Paper II, behavioural assessment (based on TDS) relied on parent-reported responses and no diagnostic interview was conducted to define mental health problems. The term 'behavioural problem' was used when referring to results obtained from the SDQ, as no diagnostic interviews were attempted to diagnose psychiatric disorders.

Neurodevelopmental disability

In the study presented in Paper II, NDD was defined as one or more of the following: CP class I–V on the GMFCS, FIQ more than 2 SDs below the reference mean value of 100 (<70 on the WPPSI-R), severe visual impairment or blindness, or need of hearing aid or complete deafness. Visual function and hearing were established during clinical examination or previous examination at public health care clinics [17].

Healthy EP/ELBW-born subjects were defined as EP/ELBW-born children with no NDD or with only minor sensory disability at age 5 years (i.e. no CP, FIQ ≥70, strabismus or refractive error, or mild hearing loss) [17].

6.2.3 Assessments at age 11 years (Papers I and II)

In 2010-11 the parents of children in the national EP/ELBW-born cohort, including the regional EP/ELBW-born cohort, and of the regional TB controls responded to a questionnaire mapping several health issues, including several aspects of PA. The regional cohort and their TB controls were invited to attend clinical examinations

including blood sampling, anthropometric measurement, and DXA scanning (Paper I). In the study presented in Paper I, PA and body composition in the regional EP/ELBW-born cohort and TB children were compared.

Questionnaire

Physical activity

Different aspects of PA were reported by parents of all participating children on completing a purpose-made questionnaire (Paper I, Table 2 and Paper II, Table 2). Information was collected on participation in sports clubs, team sports, or other PAs alone or together with family members. Parents graded their children's endurance, proficiency, clumsiness and how vigorous the child was, compared to their peers, in sports and play. In addition, the following question adapted from *the World Health Organization's Health Behaviour in Schoolchildren survey* was included to determine the frequency of leisure-time physical activity [230,231]: *Apart from at school, how often does your child usually exercise so much that it gets out of breath or sweats?* The response options were: '*Never'*, 'less than one time per week', 'one time per week', '2–3 times per week', '4–6 times per week', and 'daily' (Paper I, Table 2). The outcome from data analysis was reported as 'days per week'.

Asthma and use of asthma medication

Questions on asthma symptoms and use of asthma medication were obtained from the International Study of Asthma and Allergies in Childhood questionnaire [232].

Puberty

In the questionnaire, parents were asked to compare their children's puberty development to peers. The response options were 'delayed', 'somewhat delayed', 'similar', 'somewhat ahead', or 'ahead' of peers.

Socio-economic status

Information on the mother's level of education and single- or two-parent household was obtained by questionnaire. A high level of education was defined as completion of a minimum of 3 years in college or achieving a university degree.

Blood samples

Blood samples were collected at the consultation and was later analysed in one run at the Hormone Laboratory at Haukeland University Hospital. The following were measured: 25-hydroxy vitamin D, testosterone, oestradiol, luteinising hormone, and follicle-stimulating hormone.

Anthropometry and body composition

Height was recorded to the nearest 0.1 cm using a fixed stadiometer. Weight was measured in minimal clothing, to the nearest 0.1 kg using digital scales. Subscapular- and triceps skinfolds were measured using a Holtain Skinfold Caliper. Waist circumference was measured using a measuring tape. Body mass index (BMI: weight/height^2) was calculated as an estimate of body fat. The subscapular-to-triceps skinfold ratio (STR) and waist-to-height ratio (WHtR) were calculated as an estimate of truncal fat mass. The z-scores for anthropometric measures were calculated with reference to Norwegian growth curves [233].

Dual-energy X-ray absorptiometry scanning

DXA is an imaging method used for evaluating body composition, based on how different tissues absorb X-ray beams of two different energy levels. This creates a two-dimensional image where bone appears white, fat dark, and lean mass grey [234,235]. In this study, *whole-body less head* and regional body composition were measured, providing data on fat mass (FM), lean body mass (LBM), BMC, and BMD (BMC divided by the projected area of the scanned image) (Table 8). Values for BMC, total BMD, lower spine BMD (L1–4), and left and right total hip BMD (BMDth) were collected. BMD z-scores were calculated using sex and age-specific paediatric reference standards provided by Lunar Prodigy enCORE2009 software version 13.20.033 [139,236].

Data on fat compartments were collected as total FM, percentage of total body fat (%BF), and FM ratio (arms + legs FM/truncal FM). LBM is a measure of muscle mass, connective tissue, and internal organs. Lean mass of the extremities, also called the appendicular lean mass (ALM), is a proxy for muscle mass and correlates highly

Table 8 Body component variables in Paper I

Body components	Anthropometry	Parameters measured on DXA
Fat mass	Weight, BMI	FM, %BF, FMI
Muscle mass		LBM, LBMI, ALM, ALMI
Fat distribution	STR, WHtR	FM ratio
Bone		BMC, total BMD, BMD spine and hip

ALM, appendicular lean mass; ALMI, ALM index; %BF, percentage of total body fat; BMC, bone mineral content; BMD, bone mineral density. BMI, body mass index; FM, fat mass; FMI; FM index; LBM, lean body mass; LBMI; LBM index; STR, subscapular-to-triceps skinfold ratio; WHtR, waist-to-height ratio.

with measures of muscle volume obtained on magnetic resonance imaging [236,237]. LBM and ALM were reported. FM, LBM, and ALM were normalised for height and reported as the FM index (FMI: FM/height^2), LBM index (LBMI: LBM/ height2) and ALM index (ALMI: ALM/height^2), respectively.

Study participants were examined by trained personnel at two centres of rheumatology (Haukeland University Hospital and Stavanger University Hospital) on a Lunar Prodigy and Lunar Prodigy Advanced DXA scan (GE Medical Systems Lunar, Madison WI, USA). The matched preterm-born and the TB participants were examined at the same centre according to geographic affiliation. Daily internal calibration and weekly calibration with a local phantom provided by the manufacturer were performed.

6.2.4 Assessments at age 19 years (Paper III)

In 2018–20, the national PDA-surgery cohort, the regional EP/ELBW-born cohort, and their regional TB controls were invited to attend clinical examination which included lung function assessment and maximal exercise capacity testing. The PDA-surgery cohort was additionally investigated for LVCP and laryngeal obstruction during exercise. Paper and electronic questionnaires mapped health issues and information on PA (Paper III).

Questionnaires

The following question, modified from the European Community Respiratory Health Survey II questionnaire, served to determine the amount of PA [238-240]: '*How many hours per week do you attend sports, exercise or exert yourself so much that you get out of breath and/or sweat?'*

In addition, the following questions were developed for the project: '*Do you have breathing problems beyond normal during physical exertion*?', '*Do you make scraping sounds or other abnormal sounds from the throat during physical exertion?',* and '*Is your voice more hoarse than in others of your age?'*.

Participants in the PDA-surgery cohort answered additional questions adapted from the Voice Handicap Index with respect to voice symptoms [241]. The following question was developed for the project: '*Does your voice affect participation in singing?'*

Pulmonary function test: spirometry

Pulmonary function was assessed by spirometry with use of a Vyntus® PNEUMO spirometer (Vyaire Medical GmbH, Hoechberg, Germany) according to standardised criteria [242,243]. Measurements of FEV1 and forced vital capacity (FVC), as well as FEV_1/FVC ratio were recorded. Raw data and z-scores calculated and standardised for age, height, sex, and ethnicity according to the Global Lung Function Initiative reference equation, were reported [244].

Exercise capacity: cardiopulmonary exercise test

Peak exercise capacity was determined by a computerised incremental treadmill exercise test (Woodway PPS 55 Med, Weil am Rhein, Germany), according to a pre-set modified Bruce protocol [245] using a Vyntus CPX unit powered by SentrySuite software (Vyaire Medical GmbH, Hoechberg, Germany). Prior to each test, the flow sensor was calibrated according to the manufacturer's instructions. Speed and elevation were increased every 90 seconds from an initial slow-walking phase until maximal exhaustion signalled by the subject. Maximal intensity was defined as achieving a respiratory exchange ratio (RER) of ≥1.05 or a maximal heart rate of ≥95% of the predicted maximal HR [220,246].

Variables of airflow and gas exchange were measured breath by breath and values were averaged over 10 seconds. The percentage of the total breathing cycle (Ttot) during which inspiration took place (Ti/Ttot) was calculated from the measured inspiratory and expiratory times. Breathing reserve was the difference between calculated maximal voluntary ventilation ($FEV_1 \times 35$) and measured peak minute ventilation (VE), reported as the percentage of maximal voluntary ventilation. Peak VO_2 was reported in millilitres per kilogram per minute and as the percentage of predicted values, calculated using reference equations for age and sex from a treadmill exercise study of a large sample of Norwegian subjects [189]. Exercise performance was described by the completed distance (in metres) on the treadmill.

Examination of the larynx during exercise: the CLE test

To detect laryngeal obstruction during exercise, participants in the PDA-surgery group underwent CPET with continuous laryngoscopy. After application of topical Lidocaine Hydrochloride 40 mg/ml in one nostril, a flexible fibreoptic laryngoscope (Olympus ENF-V2®, Tokyo, Japan) with a diameter of 3.4 mm, was inserted through a tight-fit opening in a customised Rudolph mask into the pharyngeal space. A special headgear secured the body of the laryngoscope (Figure 4, page 53).

Describing inappropriate laryngeal obstruction during exercise using a modified visual score

Video recording from all CLE tests were assessed for laryngeal obstruction by an otolaryngologist and a paediatrician with extensive experience in visual score classification of CLE test, as described by Maat *et al*. [247]. Adduction of supraglottic and glottic structures of the larynx was scored, ranging from normal (0 point) to maximal adduction (3 points) at moderate (fast walking immediately before running) and maximal effort. Because of asymmetry of the laryngeal structures in subjects with LVCP, a *modified CLE score* was developed, scoring the left and right supraglottic and glottic areas separately. The total modified CLE score was the sum of all sub-scores at moderate and maximal exercise, ranging from 0 point (no adduction of left or right supraglottic or glottic structures at moderate and maximal effort) to 24 points (maximal

adduction of left and right supraglottic and glottic structures at both moderate and maximal effort) [220].

Identification of left vocal cord paralysis: laryngoscopy with stroboscopy

Participants in the PDA-surgery cohort underwent video-laryngoscopy with strobe light illumination (Laryngeal Strobe, Model 9400, Pentax Medical, Montvale, New Jersey, USA) to confirm the diagnosis of LVCP or other laryngeal pathology.

6.3 Data collection: Paper IV

The recruited participants performed spirometry and maximal treadmill exercise testing with and without CLE setup, in a randomised order, 2–4 days apart (Figure 4). The same pre-test preparations in term of food intake, hours of sleep at night, and last work-out were applied for both tests. Spirometry, CPET, and CLE tests were performed as described in Section 6.2.4 with two exceptions—the speed and elevation of the treadmill were increased every 60 seconds, and measurements of gas exchange were averaged over 30 seconds. The same digital volume transducer (flow-sensor) was used in both tests and care was taken to avoid air leakage from the face masks. CPET parameters included HR, respiratory rate (RR), RER, tidal volume (Vt), VE, peak carbon dioxide production (VCO_2), peak VO_2, and distance completed on the treadmill.

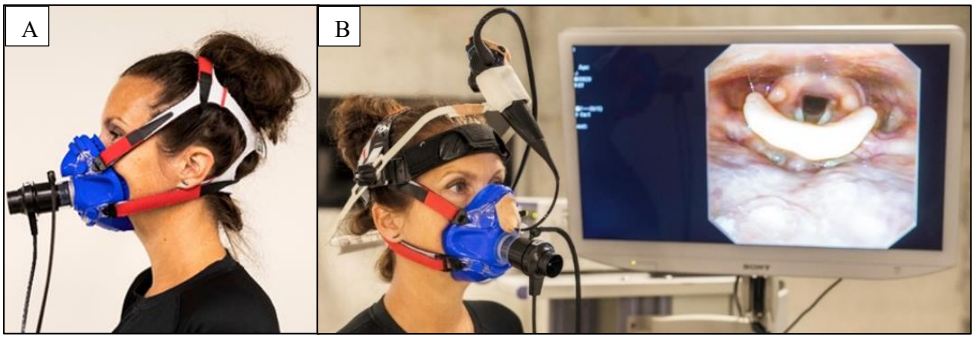

Figure 4 CLE setup. (**A**) Facemask used in ordinary CPET. (**B**) Modified face mask with a flexible transnasal laryngoscope positioned through a tight-fit opening used in the CLE test. Modified from Engan *et al. ERJ Open Res 2021*.

6.4 Statistical analysis

Descriptive statistics were presented as means with SDs for continuous variables with normal distribution or as medians with ranges for non-normally distributed data. Categorical data were presented as counts with percentages of the total. Independent groups were compared with the use of independent sample *t*-test with 95% confidence intervals (CI) for normally distributed continuous variables, the Mann-Whitney test for non-normally distributed continuous variables, and the chi-square test or Fisher's exact test for categorical variables. Normal distribution of data was determined by descriptive statistics, histograms, Q-Q plots, or the Kolmogorov-Smirnov test.

In Paper I, paired group comparisons were performed using a mixed linear model and Wilcoxon's signed-rank test. In a mixed linear regression model, the body components were adjusted for body size, stage of puberty (based on parental reports), and the PA frequency. An interaction term was constructed to test differences between the EP/ELBW-born and TB groups with respect to an association between PA frequency and body composition.

In the study presented in paper II, logistic regression analyses were used to identify possible associations of predictor variables at age 5 years (MABC5, TDS90, and FIQ70–84) with different aspects of PA in healthy-EP/ELBW born children at age 11 years. Results were presented as odds ratios (OR) with 95% CI, using crude and adjusted models.

In the study described in Paper III, analysis of covariance was used when differences in completed distance and peak VO_2 between the groups were adjusted for sex and self-reported PA (hours of exercise per week), and when differences in pulmonary function between the PDA-surgery group and the EP/ELBW-born control group were adjusted for BPD. An interaction term for sex and group affiliation was included to examine whether the difference in peak VO_2 between all EP/ELBW-born subjects and TB controls was influenced by sex. To investigate whether peak VO_2 was associated with CLE scores, a linear regression with the modified CLE score and sex as predictors was used.

In the study reported in Paper IV, a paired *t*-test was used to compare mean differences between the two methods (CPET and CLE). To estimate how far apart measurements by the two methods were likely to be, the 95% limits of agreement (LoA) were calculated (average difference ±1.96 SD of the difference) and visualised in Bland-Altman plots. One-sample *t*-test versus zero was used to assess for a systematic bias between the techniques. To test whether the difference was influenced by the magnitude of the measurement (proportional bias), the difference between the two methods was regressed on their mean value. The intraclass correlation coefficient (ICC) using a two-way mixed effect model based on single ratings and absolute agreement was calculated to determine the test–retest reliability. Values >0.6 were considered to indicate good reliability, and values >0.9 to indicate excellent reliability [248,249]. The within-subject (ws) coefficients of variation (CoV) were used to determine the reproducibility of the parameters (CoV = 100 × ws-SD/mean).

Provided an expected mean difference in peak VO_2 of 0.4 ml/kg/min, an SD of the mean difference of 1.0 ml/kg/min, and a 95% LoA set to 3.5 ml/kg/min, a minimum of 31 pairs were required (alpha values set to 0.05, power of 90%). Estimate were based on a previous study comparing peak VO_2 in CPET and CLE using bicycle ergospirometry [196]. The mean difference and SD of the difference were expected to be lower in the present study.

SPSS statistical package version 24–26 (IBM SPPS Statistics, Armonk, NY, USA) was used for all analyses and MedCalc version 19.5.3 (MedCalc Software Ltd, Osted, Belgium) was used to create some of the graphs.

A two-sided level of statistical significance was set at $p \leq 0.05$ in Papers II, III, and IV and at $p \leq 0.01$ in Paper I, as an adjustment for multiple comparisons.

7. SUMMARY OF RESULTS

7.1 Study cohort characteristics (Papers I, II and III)

Recruitment of study participants is depicted in Figure 5. Of 638 EP/ELBW-born infants, 174 were stillborn or died in the delivery room, 86 neonates died in NICU, and two were declined participation by their parents. In the period from NICU discharge to the age of 5 years, a further 4 children had died. In the period from age 5–11 years, 372 EP/ELBW-born participants were alive. About 80 % of the national cohort who survived until discharged from NICU were included based on GA <28 weeks, while almost 20% were recruited based on BW <1000 grams.

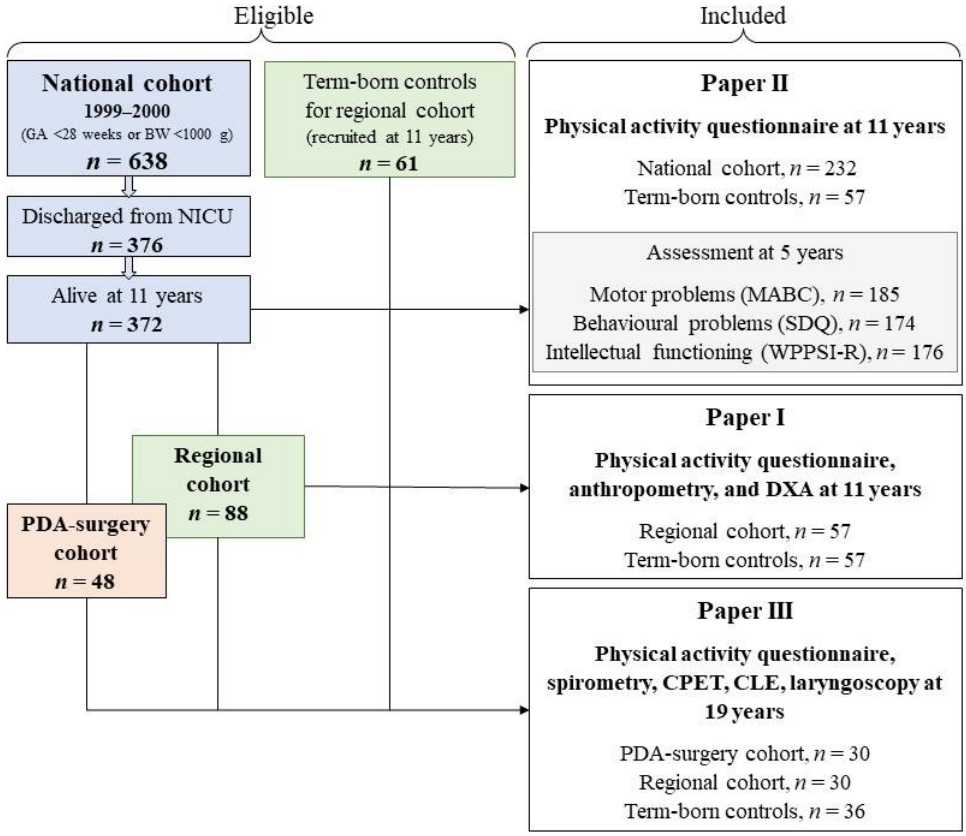

Figure 5 Flow chart showing eligible subjects and those included in the studies presented in Paper I, II and III.

7.1.1 Study subjects: Paper I

In Paper I, parental-reported information on PA and measures of body composition in EP/ELBW-born children from the regional cohort and their TB controls at age 11 years were compared. Fifty-seven of 88 (65%) eligible EP/ELBW-born children were included. Their mean BW was 840 g (range 450–1250 g) and the median GA was 27 weeks. Fifty-seven TB children were included. Table 9 provides the number of children with available information on PA and body composition measurements.

Among the EP/ELBW-born children who did not participate at age 11 years, a greater proportion received mechanical ventilation compared to those who participated. The proportion of children with BPD was similar in both groups.

7.1.2 Study subjects: Paper II

In Paper II, parental-reported information on PA was compared between EP/ELBW-born children with and those without NDD in the national cohort, as well as with regional TB children at age 11 years. Furthermore, associations between motor coordination (MABC), behavioural problems (SDQ), and intellectual functioning (WPPSI-R) at age 5 years and different aspects of PA at age 11 years were explored in the group of healthy EP/ELBW-born children.

Data on PA were available for 232 of 372 (62%) eligible EP/ELBW-born and 57 TB children. Mean BW for preterm participants was 865 g (range 450–1370 g) and median GA was 27 weeks. Results from the MABC, WPPSI-R, and SDQ assessments at age 5 years were available for 185, 176, and 174 of EP/ELBW-born children, respectively, participating at age 11 years.

Among the EP/ELBW-born children, 208/231 were classified as healthy and 23/231 as having NDD. (One participant, who did not attend examinations at age 2 and 5 years, but did participate at 11 years, was excluded from the analyses due to unknown NDD status.)

Those EP/ELBW-born children who did not participate at age 11 years (n = 140) had a higher rate of CP, blindness, or deafness at age 5 years than those who participated.

Table 9 Study sample: Paper I

Measurements at age 11 years	**EP/ELBW-born children regional cohort *(n)***	**TB controls *(n)***
Height and weight	54	54
Skin folds and waist circumference	53	50
Blood test	49	48
DXA	47	49
Questionnaire on physical activity	56	57

7.1.3 Study subjects: Paper III

In Paper III, 19-year-old young EP/ELBW-born adults with a history of neonatal PDA surgery were examined for LVCP. Voice- and respiratory symptoms, lung function, exercise capacity, and exercise-induced laryngeal obstruction were compared between subjects with and those without LVCP. Furthermore, in terms of lung function and exercise capacity, the PDA-surgery group was compared to EP/ELBW-born controls from the regional cohort who had not undergone PDA surgery, and to regional TB controls. Recruitment of participants is shown in Paper III, Figure 1.

In the national cohort, 48 subjects had undergone neonatal open PDA surgery. At age 19 years, 46 of these subjects were alive and located in Norway or abroad with known addresses. Two subjects were untraceable and had most likely moved abroad.

In the PDA-surgery group, 30 of 48 (63%) eligible subjects consented to participate. Mean BW was 792 g, and median GA was 26 weeks (range 23–29 weeks). For EP/ELBW-born controls, mean BW was 845 g and median GA was 27 weeks (range 24–31 weeks). In the PDA-surgery group, in addition to a lower GA, a greater proportion had received postnatal steroids, and were diagnosed with BPD, compared to the EP/ELBW-born control group.

For EP/ELBW-born controls, 11 subjects were diagnosed with PDA in their neonatal period. Of these, three subjects received pharmacological treatment (indomethacin) and the remaining eight received conservative treatment. The TB controls group consisted of 36 subjects.

7.2 Physical activity in EP/ELBW-born children (Papers I and II)

In Papers I and Paper II, questionnaire-based data on PA obtained at age 11 years in regional and national cohorts were analysed, and both compared to the same TB controls. Results were found to be generally similar, as described in Paper I and Paper II.

Overall, EP/ELBW-born subjects were reported to be less frequently physically active than TB children (Paper II, Figure 2). Among all EP/ELBW-born children (n = 231), 31% exercised ≤1 day/week compared to 14% of TB children. The group of healthy EP/ELBW-born children (n = 208) also reported being less physically active than TB controls (28% vs 14% exercised ≤1 day/week, respectively).

Participants' parents were asked to compare their child to their peers with respect to a number of specific questions related to PA. Healthy EP/ELBW-born children were more often reported to have lower physical endurance (36% vs 2%) and to be less vigorous (22% vs 7%), when compared to TB controls. They were also more often rated to be clumsy (32% vs 5%) and to have poor proficiency (23% vs 5%) in sports and play. Fewer healthy EP/ELBW-born children participated in team sports than TB children (48% vs 72%). This difference in team sports participation was explained by the higher proportion of participating TB boys, compared to healthy EP/ELBW-born boys (80% vs 50%). All these results remained significant after adjusting for socio-economic status (Paper II) [17].

When EP/ELBW-born children with NDD (n = 23) were compared to healthy EP/ELBW-born children, the former group were reported to have worse outcomes with respect to all questions on PA included in the questionnaire, except in terms of participation in team sports or other sport club activities (Paper II, Table 2).

7.2.1 Motor coordination problems, behavioural problems, and borderline intellectual functioning at age 5 years in relation to physical activity outcomes at age 11 years (Paper II)

Motor coordination problems

Healthy EP/ELBW-born children with motor coordination problems (MABC5, *n* = 21/170) at age 5 years had an increased risk of poor proficiency in sports activities, clumsiness, less vigorous PA, and lower endurance in PA at age 11 years (OR range 2.7–5.4). Results in terms of poor proficiency and less vigorous PA remained significant in adjusted analyses, with minor changes in OR estimates.

Behavioural problems

Healthy EP/ELBW-born children with behavioural problems (TDS90, *n* = 46/153) at age 5 years had an increased risk of poor proficiency in sports activities and clumsy gross motor function, less vigorous PA, and lower endurance in PA at age 11 years (OR range 2.2–3.9). A TDS90 was also associated with lack of participating in organised sports activities outside school. Result in terms of poor proficiency in sports activities, less vigorous PA, and lower endurance in PA remained significant in adjusted analyses, with minor changes in OR estimates.

Borderline intellectual functioning

Healthy EP/ELBW-born children with borderline intellectual functioning (FIQ70–84, *n* = 29/157) at age 5 years had an increased risk of clumsy manual dexterity, less vigorous PA, and lower endurance in PA at age 11 years (OR range of 3.1–4.1). These results remained significant in adjusted analyses, with minor changes in OR estimates.

7.3 Body composition in EP/ELBW-born children at age 11 years (Paper I)

EP/ELBW-born children had a less favourable body composition with signs of increased truncal fat distribution (lower FM ratio and higher STR), reduced skeletal muscle mass (ALM, ALMI), and decreased BMD z-scores, compared to TB controls (Figure 6). The differences in BMD z-scores and muscle mass were reduced and became statistically insignificant ($p > 0.01$) when PA frequency was adjusted for.

The mean height z-score of SGA EP/ELBW-born subjects was lower than AGA EP/ELBW-born subjects. Measures of BMD and muscle mass were also lower; however, not respective variables normalised for height (e.g. BMD z-score and ALMI).

7.3.1 Physical activity in relation to body composition

Increased PA frequency was associated with lower body fat (%BF and FMI) and higher BMDth z-scores in all participants (i.e. EP/ELBW-born and TB). Interaction analysis of the associations between PA and body composition showed an overall tendency for PA to have a less positive effect on muscle mass (ALMI) and BMDth in EP/ELBW-born children compared to TB controls.

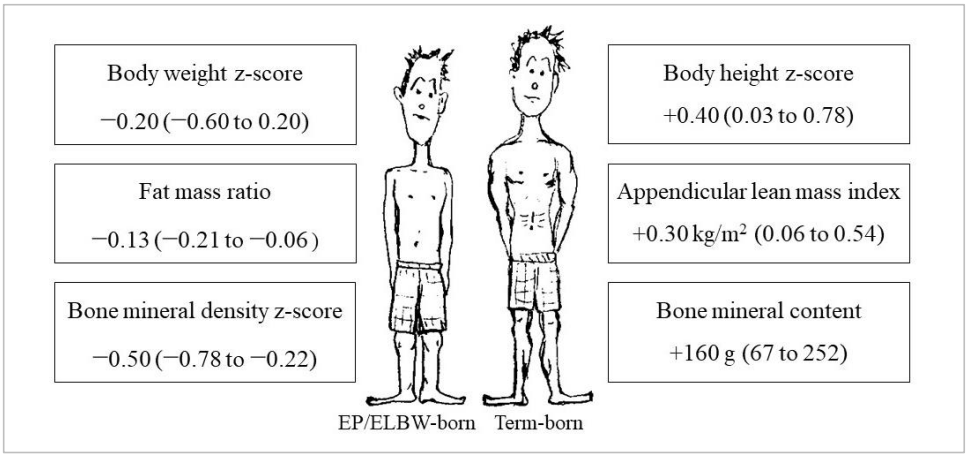

Figure 6 Crude differences (mean with 95% CI) in measures of body composition between the EP/ELBW and TB matched participants (mixed linear model). Illustrated by Mette Engan, modified from European Respiratory Society congress poster, 2018.

7.4 Neonatal PDA surgery and left vocal cord paralysis (Paper III)

At age 19 years, 16 of 30 (53%) subjects in the PDA-surgery cohort were diagnosed with LVCP. Two subjects (7%) had laryngeal stenosis in addition to LVCP. One subject (3%) presented with right-sided arytenoid prolapse with an overlying left-sided arytenoid fold making, making vocal cord assessment during phonation difficult, and thus LVCP could not be determined. Thirteen subjects (43%) had a normal laryngeal examination (i.e. no LVCP or major anatomical pathology).

7.4.1 Voice and respiratory symptoms in subjects with LVCP

Twelve of the 14 subjects diagnosed with LVCP reported one or more voice symptoms, and eight reported having a hoarse voice, or a voice that affected their participation in singing, or that limited their ability to be understood in a noisy environment. More than half reported breathing problems beyond normal during physical exertion, with no difference, however, when compared with subjects without LVCP.

7.4.2 Physical activity, lung function, and exercise capacity in relation to left vocal cord paralysis

When comparing PDA-surgery participants with LVCP and those without LVCP, no statistically significant differences were found in self-reported PA frequency, lung function parameters (z-scores for FVC, FEV_1, and FEV_1/FVC), or peak VO_2. Participants with LVCP used a higher percentage of their total breathing cycle on inspiration compared to those without LVCP.

7.4.3 Exercise-induced laryngeal obstruction in relation to LVCP

Subjects in the PDA-surgery group were assessed by the CLE test. Those with LVCP had a higher modified CLE score compared to those without LVCP (median CLE score 9 vs 4), and all but one with LVCP had a CLE score above 4, indicating laryngeal obstruction during exercise. The modified CLE score was not associated with peak VO_2 or self-reported respiratory symptoms.

7.4.4 Lung function, physical activity, and exercise capacity in young EP/ELBW-born adults

The PDA-surgery group of young adults had a lower z-scores for FVC, FEV_1, and FEV_1/FVC, compared to EP/ELBW-born children and TB controls. Mean (95% CI) difference in FEV_1 z-score between the PDA-surgery group and the EP/ELBW-born control group was 0.89 (1.17, 1.61), $p = 0.02$, after adjusting for BPD status.

Both the PDA-surgery group and the EP/ELBW-born control group reported less PA, ran a shorter distance on the treadmill, and had lower peak VO_2 compared to the TB group (Figure 7 and Table 10). The mean (95% CI) differences in completed distance and peak VO_2 between all the EP/ELBW-born participants combined, compared to TB controls were 218 (114, 322) metres, (p <0.001), and 4.9 (1.8, 8.0) ml/kg/min (p = 0.002), respectively, after adjusting for sex. There was no significant interaction effect between sex and group affiliation (all EP/ELBW and TB) on peak VO_2 (p = 0.16). When controlling for PA, the completed distance on the treadmill was still shorter for EP/ELBW-born participants, compared to TB controls (mean (95% CI) difference 150 (39, 260) metres; $p = 0.009$); however, there was no significant difference in peak VO_2 (3.2 (–0.2, 6.7) ml/kg/min, $p = 0.07$) [220].

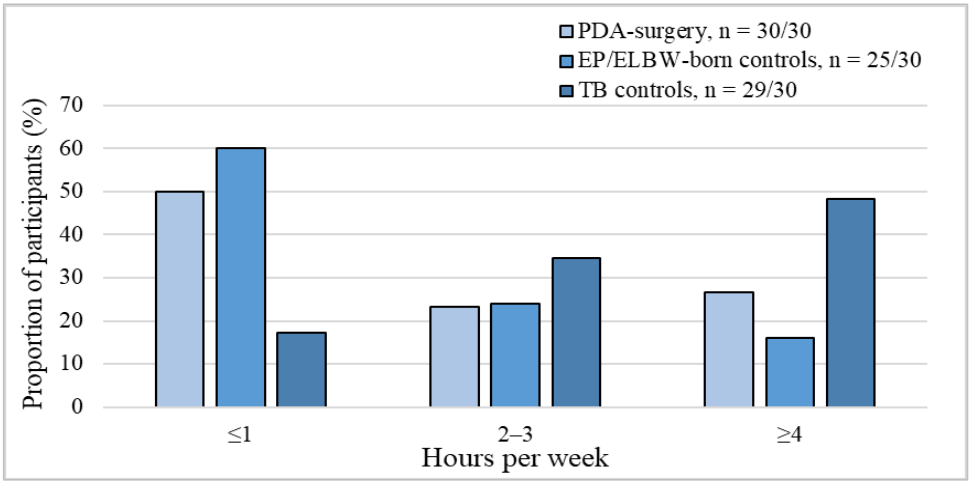

Figure 7 Self-reported PA in young EP/ELBW-born and TB adults. Modified from Engan *et al, Front Pediatr* 2022 [220].

Table 10 Lung function and exercise capacity

	PDA-surgery		**EP/ELBW-born controls**		**Term-born controls**	
	n = 26 (12 females) *		*n* = 30 (17 females)		*n* = 36 (13 females)	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
FVC, *z-score*	–0.92	–1.44, –0.40	–0.16	–0.49, 0.18	–0.10	–0.32, 0.12
FEV_1, *z-score*	–1.76	–2.31, –1.21	–0.68	–1.07, 0.29	–0.28	–0.51, –0.04
FEV_1/FVC, *z-score*	–1.50	–2.01, –0.98	–0.81	–1.20, –0.42	–0.36	–0.61, –0.11
Distance, *m*	892	805, 978	858	763, 953	1117	1017, 1216
Peak VO_2, *ml/kg/min*	37.5	34.9, 40.2	38.1	35.1, 41.1	43.6	41.0, 46.5
Peak VO_2, *% of reference*	79.6	73.5, 85.8	83.1	76.5, 89.6	90.2	85.5, 94.9

* *n* = 25 for peak VO_2

Modified from Engan *et al, Front Pediatr 2022* [220].

7.5 Reliability of maximal oxygen consumption in CPET with CLE (Paper IV)

Of 47 participants, 40 (21 females) with a mean age of 24.8 (range 15–35) years successfully completed both CPET and the CLE test. Ergospirometry data, obtained with or without CLE set-up, did not differ in paired *t*-test analyses, except for mean (95 % CI) completed distance on the treadmill which was 49 (16, 82) metres longer during CPET without CLE (Paper IV, Table 2). The agreement with 95% LoA, test–retest ICC, and within-subject CoV for the ergospirometry variables are provided in Paper IV, Table 3. The mean (95%CI) difference in peak VO_2 between CPET and the CLE test was 0.2 (–0.4, 0.8) ml/kg/min, with an agreement (95% LoA) of 0.2 ± 3.7 ml/kg/min, corresponding to an LoA of ± 6.6 % when expressed as a percentage to the mean (Figure 8).

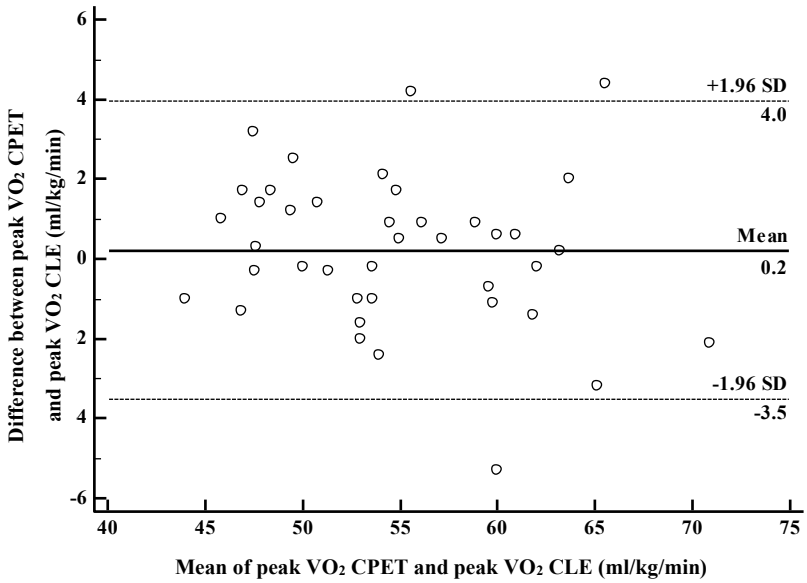

Figure 8 Bland-Altman plot illustrating agreement between peak VO_2 values obtained from CPET with and without CLE setup. Modified from Engan *et al*, *ERJ Open Res 2021*. Copyright ©ERS 2020 (CC BY-NC 4.0).

8. DISCUSSION

In this section, the methodological strengths and limitations of the studies presented in the papers included in this thesis are described. Furthermore, the main findings and implications of these studies are discussed and compared to existing knowledge in the field.

8.1 Methodological considerations (Papers I, II and III)

Biomedical research aims to generate generalisable knowledge based on the population sample being studied. To achieve this, a study should have high internal and external validity. Internal validity of a study is defined as the extent to which the observed results represent the truth in the population under study. External validity refers to the extent to which the results of a study are generalisable to the population that the study sample is intended to represent [250].

The ability of a study to achieve its aims of what it sets out to measure is dependent on many factors. These include errors in measurement of exposure and outcome variables, as well as systematic errors such as selection bias, information bias, and confounding.

8.1.1 Selection bias

Selection bias is said to occur when the participants in a study differ from the population the study aims to describe, i.e. the study has failed to ensure that the study sample is representative of the population intended to be analysed. By design, the nationwide study design on which the studies presented in this thesis were based eliminated selection bias at the time of enrolment (birth). All infants, including stillbirths, with GA <28 weeks or BW <1000 g who were born in Norway were included, and data on pregnancy and NICU stay were available for the entire cohort.

In follow-up studies, selection bias may be introduced if dropout does not occur at random. Here, at national follow-up performed at age 11 years, information related to PA was available for 62% of surviving EP/ELBW-born children; of these, 75–80% had been assessed with MABC, SDQ, and WPPSI-R at age 5 years (Paper II). EP/ELBW-

born children who did not participate in the studies at age 11 years had higher rates of CP, blindness, and deafness than participating subjects. This introduced a selection bias that might have affected the estimation of differences in PA parameters between healthy EP/ELBW-born subjects and those with NDD. A similar selection bias might have occurred also at the 5-year follow-up.

In the studies presented in Paper I, the inclusion rate for the EP/ELBW-born regional cohort was 65%. More participants than non-participants had received mechanical ventilation, however, the rate of BPD was similar in both groups. EP/ELBW-born children with limited mobility were excluded from the analysis. Therefore, results related to DXA and PA assessment have lower generalisability to *all* EP/ELBW-born individuals.

In the study presented in Paper III, 63% of young EP/ELBW-born adults who underwent neonatal PDA surgery participated in clinical assessment. More participants than non-participants had a normal neonatal cerebral ultrasound scan, suggesting selection towards more healthy participants. It is possible that the requirement for maximal exercise testing led to inclusion of participants who were more familiar with running or who considering themselves more physically fit. A similar selection bias might have affected recruitment of the TB controls.

To perform technically satisfactory spirometry and CPET, participants must be able to understand and perform correctly in the testing environment. A few subjects with severe NDD were unable to participate in pulmonary function and exercise testing. Therefore, test results related to pulmonary function and exercise capacity are not representative of *all* EP/ELBW-born subjects in the cohort. However, this should not affect comparison with other studies using the same tests, as cooperation is always required.

Historically, observational studies of preterm individuals have often used BW as an inclusion criterion. To allow comparison with other studies using a BW cut-off, and to increase the number of eligible participants, the Project Extreme Prematurity research group used BW <1000 g or GA <28 weeks as inclusion criteria. This resulted in

selection of SGA participants and with increasing severity of SGA with increasing GA above 28 weeks. Although not a selection bias per se, as this assortment of participants was expected, this composite inclusion criterion of both BW <1000 g and GA <28 weeks could challenge result interpretation.

8.1.2 Survival bias

Survival bias occurs when a group being studied for an outcome also has an increased risk of death and only survivors can be included. Notably, if this risk of death differs horizontally between institutions or longitudinally over time, studies might not be directly comparable, as varying death rates might explain variations in outcomes. For the national cohort in the studies presented here, survival to discharge from NICU for infants admitted into neonatal intensive care, was 376 of 462 infants (81%), which is comparable to other studies [53,251,252]. However, survival rates for EP neonates do change over time and vary between NICUs. This may be influenced by different attitudes towards the provision of life support to neonates perceived to be at the threshold of viability [1-3,252,253]. These changes and variations in survival rate may bias the study results presented in this thesis. Generalisability therefore is likely to be limited to EP/ELBW-born survivors born in the same era, and thus who had access to similar treatment options, with similar attitudes from health care professionals with respect to the ethics of providing life-saving treatment to the most immature neonates.

8.1.3 Control group

Unbiased inclusion of control subjects is important to obtain a reliable comparison of outcomes between exposed (preterm) and unexposed (TB) groups. A notable strength of the study presented in Paper I, was the recruitment of controls. TB subjects for the regional cohort were individually matched for age and sex with the index case to control for unknown confounders that might influence the group comparison. On average, 1.6 TB subjects had to be asked to participate for each preterm-born index case in order to recruit a full 1:1 control group, thus making the likelihood of selection bias low. This compares favourably with a broader recruitment strategy involving classmates, families, friends, or hospital staff, which is more likely to produce a biased

control group with a personal interest in the research and testing due to health problems they want to explore or perhaps health advantages they want to demonstrate.

This same control group was also used in the study presented in Paper II. Free access to health care for all children and an egalitarian social structure in Norway make regional-specific differences in children's health small. These children were therefore considered an appropriate control group also for the national cohort of EP/ELBW-born children. In the study presented in Paper III, participation rate was low in both the EP/ELBW-born control group and the TB control group, so selection bias might have occurred. No analysis was conducted to identify possible selection bias.

8.1.4 Information bias

Information bias occurs when a variable is incorrectly measured or classified. It can be caused by the observer, the study participant, or the instruments used. If participants are assigned to the wrong outcome category, the estimate of the association between exposure and outcome will be incorrect.

Gestational age and birthweight

The main exposure and inclusion criteria in the studies constituting this thesis, were birth before 28 weeks' gestation and BW below 1000 g. In 95% of the national cohort, routine ultrasound examination at 17–18 post-menstrual weeks was used to determine GA [254]. In the remaining cases, GA was determined using the date of the mother's last menstrual period, which is considered a less reliable method. Estimation of GA by ultrasonography in the first part of the second trimester is based on a combination of fetal biometric measurements. This estimate has been reported to have an error of less than 7 days when compared with GA obtained from in vitro fertilisations [255]. BW measurement is routinely performed on all newborns shortly after birth and can be associated with a small measurement error depending on the scale used and additional potential operator errors. It is possible that measurement errors in determining BW and GA might have occurred, resulting in incorrect recruitment to the cohort. Assuming that these errors occurred infrequently and randomly, the biological effect of possible misclassification in terms of being eligible for the study or not, is likely to be small.

Psychometric properties of tests (Paper II)

A major strength of the study was the use of standardised and reliable tests that are validated and widely used to assess neurodevelopmental and behavioural problems.

The GMFCS has excellent interrater (agreement among test personnel) and test–retest reliability (ICC >0.90) and correlates strongly with other classification systems with respect to CP [256]. The MABC is widely used to identify children with DCD and has a good test–retest reliability with reported ICC of 0.77–0.95 [257,258] and interrater agreement for classification into a similar risk group at 73–97 % [226,227]. The MABC correlates strongly with other tests of motor function [257].

According to the WPPSI-R manual, WPPSI-R has an interrater agreement in the range of 0.88–0.96. The measurement of FIQ has strong stability, with a reported test–retest correlation coefficient of 0.91 [131,259]. The correlation between WPPSI-R and other tests of intellectual functioning is moderate to strong [259].

The SDQ has good psychometric properties and is frequently used when assessing mental health in EP/ELBW-born children [260-262]. Abnormal parental-reported TDS have shown acceptable agreement with the presence of a psychiatric disorder (Cohen's kappa = 0.47) [263]. When parents respond to the SDQ, the test–retest correlation coefficient for TDS is reported to be 0.76. The correlation between the TDS and similar total scores in comparable tests is strong [262] .

Interrater agreement was not assessed among the paediatricians, psychologists, and physiotherapists who carried out the above tests at the 19 participating paediatric departments. However, given the test properties described above, information bias affecting the classification of NDD status and the prediction of PA outcome at age 11 years was likely low.

Physical activity questionnaire (Papers I, II and III)

A strength of the PA assessment described in Papers I and II was that multiple aspects of PA were examined. The question on PA frequency *('Apart from at school, how often does your child usually exercise so much that it gets out of breath or sweats?')* was

adapted from the World Health Organization's *Health Behaviour in Schoolchildren Survey* [230,231]. In adolescents aged 13–18 years, a similar question has been shown to have good test–retest reliability (ICC of 0.73) and modest validity (correlation with peak VO_2 of $r = 0.39$) [230]. However, participants in the studies presented in Papers I and II were only 11 years old and the reliability and validity of proxy reports in this age group might differ from that of self-reports in older adolescents. In general, correlation between proxy reports and objective measures of PA has been reported to range from none to moderately strong [264].

In Paper III, data on duration of PA were collected as self-reported responses to the question '*How many hours per week do you attend sports, exercise or exert yourself so much that you get out of breath and/or sweats*?'. In 16- to 18-year-old adolescents, a similar question yielded a test–retest ICC of 0.85 (0.70–0.93) and a modest correlation with peak VO_2 ($r = 0.33$) [230].

Except for the question about PA frequency, the reliability and validity of questions related to PA in the studies in Papers I and II were unknown. Additional objective measurement of the frequency, intensity, and duration of PA would have been valuable. Parental responses might have been biased by incomplete review and inadequate recall of their child's activities. In addition, parents of EP/ELBW-born children might been more aware of health problems and thus recall more easily symptoms and difficulties that could be related to preterm birth.

Reliability of bone mineral density assessment (Paper I)

DXA scanning has been found to be highly accurate in *in*-vivo studies [265], with high repeatability, with reported CoV in the range of 1–2% for whole-body measures of BMD, lean mass and FM. Measures of regional body composition are less precise, with measures of regional FM being the most inaccurate (reported CoV of up to 5%) [234].

Bone mass is associated with body size and maturation. A limitation of the study described in Paper I was the puberty assessment. Pubertal staging by the Tanner scale would have been preferable. However, the prospect of such an intimate examination

could have deterred study participation, thereby potentially introducing a new risk for biased inclusion.

Studies have suggested an association between early pubertal onset and preterm birth. A recent meta-analysis concluded that preterm-born children enter puberty at the same age as TB children [266], supporting the present study findings from the questionnaire-based puberty assessment reported in Paper I.

Dietary intake of calcium and vitamin D, both important determinants of bone mineral accrual [267], was not recorded. However, there was no difference in serum levels of 25-hydroxy vitamin D detected between the groups.

DXA-derived BMD is based on a two-dimensional projected area of a three-dimensional structure. In regression analyses, the z-scores for weight and height were included to adjust for the difference in body size between EP/ELBW-born children and TB controls. However, it remains possible that differences in bone size were not fully accounted for and that smaller bones were found to have lower BMD than larger bones [268].

8.1.5 Confounders and mediators

A confounder is an extraneous variable that is correlated with both the exposure and the outcome variable. If a confounder is not taken into account when analysing of relationship between the exposure and the outcome, the result will be biased because the effect of the exposure is mixed with the effect of the confounding variable. A mediator is a variable that mediates the relationship between the exposure variable and the outcome variable. The mediator should be taken into account in the analysis if only the direct effect of the exposure variable on the outcome is of interest. The mediator should be omitted from the analysis if the total effect is of interest. Several approaches to identify confounding factors and mediators have been described [269]. In the studies presented in this thesis, the independent variables in the regression analyses were selected based on a clinical and empirical understanding of factors known to, or assumed to be, associated with the exposure and outcome variables.

In the mixed linear regression analyses comparing body composition between EP/ELBW-born subjects and TB controls, the outcome was adjusted for body size, pubertal development, and for PA frequency. All these factors are known to mediate the outcome variables, thereby distorting the direct association between EP/ELBW-born subjects and TB controls (Paper I).

In the study described in Paper III, the difference in peak VO_2 between EP/ELBW-born children and TB controls was adjusted for unequal sex distribution between the compared groups, as males are known to have a higher peak VO_2 than females [189]. Finally, self-reported PA frequency was added as a covariate because it has a mediating effect on peak VO_2.

Socio-economic inequality in preterm birth is a consistent finding, and preterm birth rates increase with increasing socio-economic disadvantage [270,271]. Low level of PA has been associated with low socio-economic status, particularly in relation to PA outside of the school setting [272]. In the study reported in Paper I, low socio-economic status (defined as attainment of low maternal education level and single parenthood) was adjusted for in the analysis of the association between EP/ELBW birth and PA frequency. Furthermore, low maternal education level was associated with motor coordination problems, behavioural problems, and borderline intellectual functioning, as well as the outcome variables for frequency of PA (*PA ≤1 day/week* and *participation in organised sports*) and was therefore adjusted for in the logistic regression analyses for these outcomes (Paper II). However, it is possible that socio-economic status was inadequately accounted for because other relevant information, such as household income, was not available.

Motor delays are partly explained by level of intellectual ability although normal and abnormal motor coordination can be observed at all IQ levels [273]. Because of this association between IQ and motor coordination, the outcomes of *clumsiness* and *poor proficiency* were adjusted for borderline intellectual functioning (FIQ70-84) in the adjusted logistic regression models. Motor coordination difficulties (MABC5) were

also adjusted for when examining borderline intellectual functioning as a possible predictor.

Preterm birth is associated with asthma or asthma-like symptoms in childhood [107] and in general, such respiratory symptoms could affect children's endurance and intensity in sports and play [274]. Asthma has also been associated with emotional comorbidities [275], and in the preterm population, associations with neurodevelopmental problems and lung disease have been noted [276]. The use of asthma medication was adjusted for in the logistic regression analysis of the outcome variables *less vigorous* and *low endurance*, to account for the possible effect of lung disease on these outcomes (Paper II).

Infants born preterm and SGA, and infants diagnosed with BPD have been found to have poorer motor outcomes [277,278]. SGA was associated with the outcome variable *dexterity* and was accounted for in the prediction analysis on this outcome. And likewise for the outcome *low proficiency,* BPD was added as a covariate (Paper II).

8.1.6 Reliability of cardiopulmonary exercise testing in young EP/ELBW-born adults (Paper III)

Various methods are used to examine maximal exercise capacity. Of these, the 20-metre shuttle run test provides an estimate of peak VO_2 and the maximal cycle ergometer and treadmill tests, for which a range of test protocols are available, provide direct measures of oxygen consumption [191,279].

Individuals born preterm may suffer from various neurosensory sequelae. In the study described in Paper III, a test protocol that was easy to understand and adhere to was chosen to minimise the risk of participants not being able to demonstrate their maximal exercise capacity. CPET performed using a treadmill was preferred to obtain direct measurements of oxygen uptake and because walking and running are familiar activities that are part of many activities of daily living. Moreover, it is easier to motivate subjects to continue until maximal exhaustion on a treadmill test than on a 20-metre shuttle run test because of relatively lesser demands on attention and cooperation.

Young EP/ELBW-born adults who had previous PDA surgery underwent CPET with added CLE setup. Participants were able to cope with the testing demands and completed technically satisfactory maximal exercise tests.

The CPET results in the PDA-surgery group were compared to results in the EP/ELBW-born and TB control groups who performed CPET without CLE setup. In the study presented in Paper IV, no systematic bias was identified in terms of peak VO_2 measurements obtained during CPET with and without CLE setup. However, during ordinary CPET, participants ran, on average, 49 metres longer than during CPET with CLE test. Given the results reported in Paper IV, direct comparison of peak VO_2 between the groups studied in Paper III is possible, although comparison of completed distance on the treadmill could be affected by systematically lower values in the PDA-surgery group.

8.2 Discussion of main results in Papers I, II and III

Results presented in this thesis showed that 11-year-old EP/ELBW children and young adults were less physically active than TB controls, and that NDD was associated with worse outcome in relation to PA at age 11 years. There was a tendency for PA frequency to have less positive effects on muscle mass and BMD in EP/ELBW-born children compared to TB children. In EP/ELBW-born children at age 5 years, motor coordination problems, behavioural problems and borderline intellectual functioning predicted poorer outcome related to PA performance at age 11 years. LVCP was common in young EP/ELBW-born with a previous history of PDA surgery. However, LVCP was not associated with reduced lung function or reduced peak VO_2. As a group, EP/ELBW-born individuals who underwent PDA surgery reported less PA and had reduced lung function and exercise capacity, compared to TB controls.

8.2.1 Physical activity in EP/ELBW-born individuals (Papers I, II and III)

The studies presented in this thesis found that schoolchildren and young adults with a history of EP/ELBW birth were less physically active than TB controls. This finding contradicts what has been reported in some studies [163,204,280] while consistent with others [12,13,281]. Overall, there are only a few studies assessing PA following VP/VLBW or EP/ELBW birth. PA is often not the main outcome and rather is reported and discussed as an additional element in studies on lung function or exercise capacity. Moreover, data on PA are not collected or reported in a standardised manner, which challenges direct comparison across studies.

Tables 2, 3 and 4 (pp. 97-9) provide an overview of studies that compare PA in VP/VLBW- and EP/ELBW-born subjects to those of TB controls. A lower level in self-reported PA among preterm-born adults compared to TB adults seems to be fairly consistent, whereas studies in childhood more often report similar levels of PA between the groups. The same trend is not seen with respect to PA data obtained by accelerometry, albeit from a limited number of studies [203-209,282,283].

The reported deficit in PA varies across studies. Kilbride *et al.* [13] compared 50 ELBW-born subjects born in the 1980s without apparent neurodevelopmental or pulmonary

disabilities to 25 TB controls at a mean age of 11 years. None of the TB controls reported being *only occasionally physically active* or *inactive,* compared to 17% of the ELBW-born children. This is comparable with results discussed in Paper II, showing that 28% of healthy EP/ELBW-born children and 14% of the TB children were physically active ≤1 day per week outside school.

Studies on PA in children measured by accelerometry have reported findings ranging from no difference to 40 minutes less of PA, and 20 minutes less of moderate to vigorous PA per day [283,284]. Some have observed poorer outcomes only in boys born preterm. A modest reduction in moderate to vigorous PA of 9 minutes per day among VP-born boys was observed by Lowe *et al.* [282], whereas Svedenkrans *et al.* reported 25 minutes less moderate to vigorous PA per day for EP-born boys [206]. A lower rate of participation in team sports among EP/ELBW-born boys, compared to TB boys, was found in the studies described in Paper I and II. This gender difference is in line with the general worse outcomes reported for males after preterm birth [285]. However, given that boys are usually more physically active than girls, a difference in PA level for preterm-born girls compared to TB girls, might not be apparent in societies where the level of PA is generally low.

Most studies have found that VP/VLBW- or EP/ELBW-born adults are less physically active than TB controls. In Paper III, results showed that 50% of young EP/ELBW-born adults engaged in PA for ≥2–3 hours per week, compared to 83% in the TB group. Similar differences, although at generally lower levels of PA, have been reported by Rogers *et al.* [281] and Caskey *et al*. [286]. Clemm *et al.* [287] did, however, report a similar level of PA among EP/ELBW-born and TB adults born in Norway during 1982-85.

The World Health Organization's recommendations for PA state that children should undertake 1 hour of PA per day, and adults 2.5–5 hours of PA per week. In this present study, information on PA during school hours was not reported, hence, comparison to the recommended level of PA was not possible. Further, among EP/ELBW-born adults, half of the study participants reported undertaking PA for ≤1 hour per week, which is far from the recommended levels of PA.

In the studies presented here, EP/ELBW-born children were more often reported to be less vigorous and to have lower endurance, compared to TB controls. Preterm-born children were also more often considered to be clumsy and to have poor proficiency in play and sports. This is consistent with other studies reporting lower exercise capacity, motor coordination problems, and difficulties in PA among children born preterm [204,214,217]. Low level of engagement in PA and poor exercise capacity may bidirectionally exacerbate and negatively reinforce each other. Therefore, measures to improve participation in PA during childhood to establish life-long positive habits of PA would prove important in the EP/ELBW-born population.

Physical activity in relation to neurodevelopmental disabilities (Paper II)

PA plays a role in increasing functional independence and improve integration and quality of life for children with disabilities. Despite these benefits, children with physical or cognitive impairments have been shown to be less physically active than children with normally development [288-290]. This is in line with results presented in Paper II showing lower PA frequency among EP/ELBW-born subjects with NDD, compared to the healthy EP/ELBW-born children, although the rate of participation in team and other organised sports did not differ. Furthermore, EP/ELBW-born children with NDD were more often rated as being clumsy and less vigorous and as having poor proficiency and lower endurance during play and sports, compared to healthy EP/ELBW-born children. Some of these findings may be explained by the nature of the children's disability, although low levels of PA may also contribute directly to impaired endurance and poorer proficiency in sports.

Several barriers, as well as facilitators, associated with participation in PA in children with physical disabilities have been identified [291]. Parental concern for the children's safety, poor motivation, and lack of skills are some examples of barriers. Examples of facilitating factors include accepting the disability, parental encouragement and motivation, and having access to the necessary equipment [291]. Exploring an individual's perspective would likely aid in enhancing participation in PA.

8.2.2 Physical activity in relation to motor coordination problems, behavioural problems, and borderline intellectual functioning (Paper II)

Motor coordination problems and physical activity

Children with motor coordination problems have been shown to be less physically active and to have lower fitness levels compared to their peers [177], with the fitness deficit not fully explained by lower levels of PA [292]. This has also been shown in ELBW-born children.

An Australian research group investigated the impact of motor coordination problems on fitness in 11- to 13-year-old ELBW children born in 1992–94. The study, which included 54 ELBW-born children and 55 TB controls, found that motor coordination problems were a predictor of exercise capacity both in the ELBW-born and TB control groups [214]. Another study from Sydney, Australia, examined 323 8-year-old children without NDD born at GA <30 during 1987-94. Fewer children in the group with motor coordination problems participated in organised sports activities after school hours, compared to the group of children with normal motor coordination [293]. The authors suggested that participation withdrawal due to motor difficulties, or through exclusion by peers, may explain the difference in PA participation. These results are partly in agreement with the findings discussed in Paper II showing an association between motor coordination problems identified at age 5 years and lower endurance and less vigorous PA at age 11 years. However, no significant association between motor coordination problems and low levels of PA (PA frequency ≤1 day/week) or participation in organised sports activities was found. This might reflect a difference among societies in the assortment of sports activities, or differences in social acceptance of motor coordination difficulties.

Behavioural problems and physical activity

PA during childhood often occurs in social contexts. As such, children's ability to interact with other children and develop friendships may be important for their engagement in PA. Danks *et al*. investigated exercise capacity and behavioural problems in 48 non-disabled ELBW-born children aged 11–13 years and 55 TB controls born during 1992–94 [294]. An association was found between exercise capacity

and social competence for both the ELBW-born and TB groups. The authors suggested that poor exercise capacity in ELBW-born population is a barrier to participation in activities that would likely promote the development of competencies in general [294].

In the study presented in Paper II, healthy EP/ELBW-born children with behavioural problems at age 5 years had an increased risk of being rated as having lower endurance, poor proficiency and being less vigorous in PA than those with a normal TDS. They also had an increased risk of not participating in organised sports activities at 11 years of age (p = 0.06 in adjusted analysis). Given the susceptibility to less engagement in PA in the EP/ELBW-born population, it would follow that particular attention should be given to those exhibiting behavioural problems in order to promote PA participation.

Intellectual abilities and physical activity

Children with intellectual disabilities have lower exercise capacity and reduced muscular strength than children with normal development [295]. An association between cognitive function and exercise capacity has also been described for the population born preterm [296]. Using data from the Swedish Conscript Register, Svedenkrans *et al.* found that in healthy young men born preterm during 1973–83, low exercise capacity, defined as the maximal load achieved on the cycle ergometer test, was associated with lower scores on the cognitive function test [296]. As discussed in Paper II, preschool borderline intellectual functioning was associated with worse PA outcomes in later years in childhood, including lower endurance and being less vigorous during PA. Furthermore, preschool borderline intellectual functioning was found to be associated with poor fine motor skills, but not with gross motor function. This is consistent with a study by Vuijk *et al*. who reported that children with mild or borderline cognitive functioning have more severe deficits in fine motor skills than in gross motor skills [297].

Research has shown that exercise may recruit and activate molecular and cellular mechanisms that prepare the brain to encode meaningful information, or cues, from the environment and protect the brain from damage [298]. A systematic review of intervention studies that investigated the effects of PA concluded that PA has a positive effect on executive function, attention, and academic performance in pre-adolescent children [299].

Thus, improving participation in PA among EP/ELBW-born children would prove benefit that extend beyond the physical effects of exercise.

8.2.3 Anthropometry, body composition, and bone mineral density in EP/ELBW-born children (Paper I)

Anthropometry

A few longitudinal studies have investigated growth trajectories of EP- and ELBW-born infants who were born in the late 1970s to early 1980s [300,301] and early 1990s [302], into adulthood. The finding of a height disadvantage for EP/ELBW-born subjects has remained consistent. Growth failure during infancy, followed by accelerated weight gain through adolescence, has been observed, resulting in BMIs comparable to TB peers. Farooqi *et al.* investigated growth in 10- to 12-year-old children born during 1990-92 in Sweden and found differences in weight and height z-scores of approximately 0.4 and 0.6 respectively, between EP-born subjects and TB controls [138]. These growth deficits are larger than results reported in Paper I for EP/ELBW children born during 1999-2000. Differences between study populations and reference values used for growth parameters could explain some of the discrepancies in outcome. Of note, TB controls in the Swedish study had a higher z-score for weight than study results from Paper I. Increased awareness of optimal nutrition during the neonatal period, as well as during infancy, might have led to improved growth outcomes in later studies.

Body composition and cardiometabolic risk

The cluster of co-occurring central adiposity, insulin resistance, dyslipidaemia, and hypertension is known as the metabolic syndrome [303]. These individual conditions are all risk factors for cardiovascular disease and type 2 diabetes [304-306]. Skeletal muscle mass serves important metabolic functions, including maintaining and improving the body's insulin sensitivity [307] and resting energy expenditure [308]. Hence, reduced skeletal muscle mass may lead to excess weight gain and the risk of developing insulin resistance and type 2 diabetes [309].

The body composition profile observed in EP/ELBW-born children in the study presented in Paper I, with lower lean mass and higher truncal fat indices, compared to

TB controls, imply an increased risk of future cardiometabolic disease. When adjusted for body size, the difference in muscle mass (ALM) was just below 1 kg, which corresponds to a difference of less than 10 % (Paper I, Table 4). It is difficult to estimate the possible impact of a muscle mass deficit of this magnitude on later health outcomes. Reduced muscle mass and higher truncal fat indices were not accompanied by higher %BF. Other biomarkers of cardiometabolic risk were not assessed. It is possible that the less favourable body composition in childhood could persist into adulthood and influence metabolic function, however, this was not investigated in this cohort.

Bone mass

There are concerns that preterm-born subjects are at increased risk of developing osteoporosis when they grow old. Reduced bone mass and BMD have been described in VLBW adults born before the 1990s, when compared to TB subjects [101,102,310]. Hovi *et al.* found a graded relationship between GA and BMD, with increasing values for area BMD z-scores in the range of 0.13–0.19 for each additional week of gestation [101]. For EP/ELBW adults born in the early 1990s, a deficit in z-scores for lumbar spine BMD and BMDth in the range of 0.2–0.3 has been described [154].

As discussed in Paper I, EP/ELBW-born children had z-scores for total BMD and BMDth that were within the normal range, but 0.3–0.4 units lower compared to TB controls, when body size and puberty were adjusted for. These results are consistent with a reduction in BMDth of 0.04 g/cm^2 found by others in 8-year-old VP born children [152,153], although in disagreement with another study that reported similar total BMD in both ELBW-born adolescents and TB controls [156].

The observed deficit in BMD for EP/ELBW-born children suggests a risk of achieving a reduced peak bone mass, and subsequently an increased risk of osteoporosis and fractures later in life. However, it is possible that EP/ELBW-born children would manage to catch up during their growth spurt, thus attaining a peak bone mass similar to controls. Follow-up through the age of peak bone mass and in older ages is needed to establish the risk of osteoporosis in the EP/ELBW population born in the post surfactant era.

Physical activity and body composition

In the general population, PA during childhood and adolescence is associated with enhanced bone mass accrual, increased muscle mass and strength, and prevention of excess weight gain and obesity [171,311]. In the study presented in Paper I, differences in BMD and muscle mass (ALM) between EP/ELBW-born children and TB controls were reduced and no longer statistically significant ($p > 0.01$) when the analysis was adjusted for PA frequency (Paper I, Table 4). Hence, reduced PA in the EP/ELBW-born group seems to mediate some of the observed differences in body composition, although firm evidence regarding cause and effect could not be ascertained. Interaction analyses suggested that the association between PA frequency and muscle mass and BMD is weaker in EP/ELBW-born children than in TB controls. This is supported by the finding that EP/ELBW-born children were reported to be less vigorous and to have lower endurance in PA. Hence, is it possible that EP/ELBW-born children may not gain similar physiological benefits when attending PA as TB peers. Intervention studies are needed to confirm whether preterm individuals gain similar positive effects on bone mass and muscle mass from PA as TB peers.

Small for gestational age

The study population in the present study consisted of EP- and ELBW-born children, resulting in a relatively high proportion of participants born SGA. Growth in preterm subjects who are born SGA is affected by the combined effects of preterm birth and SGA status, and they often represent the smaller individuals of the ELBW population later in life [137]. SGA may be regarded as a proxy marker of intrauterine growth restriction when the intrauterine growth rate is unknown. In this present study, BW below the 10th percentile was considered SGA. To avoid misclassifying those with constitutionally low BW, a lower cut-off for SGA, i.e. less than 2 SDs below normal BW for GA, would have been preferable according to a consensus statement from 2007 [312], although not commonly used in follow-up studies after preterm birth.

As presented in Paper I, the group of SGA preterm-born subjects were shorter than AGA preterm-born subjects, and muscle mass and BMD were also reduced. These results were not statistically significant when comparing the respective values

normalised by height or z-values. Analyses including only AGA EP/ELBW-born subjects and TB controls were not performed; hence, the separate effects of SGA and EP/ELBW birth could not be determined.

8.2.4 Left vocal cord paralysis (Paper III)

Prevalence

Open surgical PDA closure may lead to iatrogenic LRL nerve injury and LVCP. Studies investigating LVCP by routine post-operative laryngoscopy after PDA surgery in EP-born neonates have found LVCP in 11–67% of cases [313,314]. A meta-analysis reported a pooled incidence of LVCP of 32% [315]. In the study described in Paper III, of 30 EP/ELBW-born adults with a history of neonatal PDA surgery, 16 (53%) were diagnosed with LVCP.

There may be several reasons underlying the relatively high prevalence of LVCP in this Norwegian cohort of EP/ELBW-born adults who underwent neonatal PDA surgery. The associations between PDA surgery, LRL nerve injury, and expected symptoms were explained in the study invitation letter. It is possible that individuals who experienced voice or breathing problems were more likely to accept invitation to participate than those without such symptoms. This possible selection bias could have led to a higher prevalence than the actual 'true' prevalence. However, if all non-participating subjects did not have LVCP, the prevalence would have been 33% (16/48), which is still relatively high. Another possible explanation for the relatively high prevalence of LVCP is that this study was performed on cooperative adult individuals with a larger anatomy that was easy to visualise by laryngoscopy. Performing a laryngological examination on neonates is challenging. Consequently, there is a risk that pathology may be overlooked, which would lead to an underestimation of the true incidence of LVCP [316].

Surgical ligation, compared to clipping, has been associated with higher rates of post-operative LVCP [317]. In the study described in Paper III, information on the type of surgery was not collected. Therefore, it is not possible to assess whether surgical technique could be another factor contributing to the high prevalence of LVCP.

Left vocal cord paralysis and symptoms

Unilateral vocal cord paralysis has been associated with social limitations and reduced health-related quality of life [318]. This is in line with results presented in Paper III, showing that many of the subjects with LVCP reported that their voice affected their participation in schoolwork, singing and in social activities. However, about one-third of subjects without LVCP also complained of voice symptoms, reflecting the relatively high prevalence of voice abnormalities reported in EP-born subjects [319].

A limitation of the study in Paper III was the small sample size. Therefore, it is not possible to draw robust conclusions about differences in voice or breathing symptoms between those with and those without LVCP. Nevertheless, the findings indicate that clinicians should consider upper airway assessment when voice and respiratory symptoms are reported by preterm-born subjects with a history of PDA surgery [219]. For subjects with LVCP, surgical treatment and voice therapy may improve voice quality [320].

Left vocal cord paralysis in relation to lung function, laryngeal obstruction during exercise, and exercise capacity

A former study on EP-born adults who underwent previous neonatal PDA surgery raised the question of whether LVCP appearing in the neonatal period may play a part in long-term development of airway obstruction in this population [219]. The results presented in Paper III do not support these findings, although the power to detect differences in airway obstruction between those with and those without LVCP, as measured by FEV_1, was limited by the small sample size.

In individuals with LVCP, the para-median position of a paralysed left vocal cord could interfere with normal exercise-induced dilatation of the glottis [321]. This, in turn, could potentially compromise airflow capacity and affect peak VO_2.

In the study discussed in Paper III, laryngoscopy during exercise revealed an additional laryngeal collapse in several subjects with LVCP; however, an exercise-induced laryngeal obstruction was also observed in subjects without LVCP. Peak VE and breathing reserve did not differ significantly between those with or those without

LVCP; however, there was a trend towards lower VE, at least in female subjects, in participants with LVCP. This finding may indicate that LVCP constitutes an obstacle to high-volume ventilation, due to either a subjective experience of dyspnoea or a physical hindrance to inspiration, the latter correlating with higher Ti/Ttot observed in the group with LVCP. The sample size was small, with wide confidence intervals for mean differences, so no firm conclusions could be made. Neither the presence of LVCP nor the modified CLE score was associated with peak VO_2. To further explore the impact of laryngeal obstruction during exercise, measuring trans-laryngeal airway resistance during exercise is a promising step forward in this area of respiratory medicine [322].

8.2.5 Lung function in EP/ELBW-born adults with a history of neonatal PDA surgery (Paper III)

In the PDA-surgery group, a higher proportion of subjects had BPD, with poorer lung function compared to the EP/ELBW-born control group. Preterm-born survivors with or without BPD are at increased risk of reduced lung function in adulthood [110]. An association between BPD and PDA surgery has been reported previously [323] and may be explained by more severe neonatal respiratory illness. PDA surgery is often performed as a last resort in infants with already advanced lung disease and/or failed pharmacological treatment of PDA [46]. However, results from animal studies support a causative pathway between PDA ligation and the development of chronic lung disease via increased expression of genes involved in pulmonary inflammation and decreased alveolar fluid clearance [324]. Re-examination of a randomised controlled trial studying the effects of prophylactic PDA ligation versus delayed ligation found a significant increase in BPD incidence in those who underwent ligation [325].

Although the association between PDA surgery and BPD is not fully understood, results from the present study imply that the subgroup of EP/ELBW-born adults with a history of PDA surgery may need special attention through follow-up to monitor their lung function. Population studies have shown that lung function follows a trajectory throughout the lifespan. Parallel to childhood growth, an increase in maximal expiratory airflow is observed before a plateau is reached at age 20–25 years, which is

then followed by a decline later in life [326]. Achieving a sub-optimal peak lung function and an excessive rate of decline in the ageing lung may eventually result in pulmonary symptoms and chronic obstructive pulmonary disease in adulthood [327].

A study limitation was that information on tobacco smoking habits was not collected. Cigarette smoking has been associated with mild airway obstruction in adolescents [328] and might have influenced the spirometry results in this study.

8.2.6 Exercise capacity in EP/ELBW-born adults (Paper III)

In the study described in Paper III, a modest deficit in peak VO_2 of approximately 5 ml/kg/min was found in young EP/ELBW-born adults compared to TB controls. LVCP or PDA surgery was not associated with poorer outcomes.

A few studies have compared exercise capacity in EP/ELBW- or VP/VLBW-born adults to TB controls (Table 5, pp. 100-02). However, the number of such studies is limited and direct comparison across studies is not possible because of differences in test protocols and different ages of participants. Overall, reductions in peak VO_2 in the range of 0–10 ml/kg/min or approximately 0–25% have been reported. Seemingly, there is no clear trend across time periods. In the various studies, both preterm-born and TB groups showed a wide range in mean values for peak VO_2. Studies using treadmill protocols generally reported higher mean values for peak VO_2.

As described earlier, several causes for modest deficits in peak VO_2 observed in the preterm-born population have been proposed. In line with finding presented in Paper III, some studies have suggested that reduced PA, and hence reduced fitness, would explain the observed deficit in exercise capacity in preterm-born adults [14,15], whereas others have not found such an association [213]. Even though endurance exercise training has been found to improve peak VO_2 in the general adult population [329], extrapolation of this association to preterm-born adults born might be incorrect. Intervention studies are needed to clearly establish the benefits of PA for EP/ELBW-born individuals.

Sex

Some studies have suggested that male preterm-born survivors have a greater reduction in peak VO_2, compared to their females counterparts; however, small sample sizes have hampered firm statistical evidence in support of this finding [14]. In the study discussed in Paper III, the interaction analysis showed a trend towards a worse outcome, albeit not statistically significant, in terms of a worse outcome in male preterm-born participants (Paper III, Figure 2). Future studies should aim to recruit a sufficient number of subjects that would enable researchers to determine possible disadvantages of a male preterm-born status, so personalised health care can be improved.

8.2.7 Relevance and clinical implications of study findings (Papers I, II and III)

The studies presented in this thesis adds to existing knowledge on PA in EP/ELBW-born children and young adults and identify early predictors of poor PA outcome—a necessary step in the development of timely interventions to promote PA. Health care providers should consider assessing PA in EP/ELBW-born individuals given their susceptibility to being less physically active. EP/ELBW-born preschool children with problems such as impaired motor coordination, behavioural problems, and borderline intellectual functioning may face challenges later in life related to being clumsy and less vigorous, as well as having reduced endurance and poor proficiency, when engaging in PA. Furthermore, study results presented in this thesis suggest that EP/ELBW-born subjects have a less favourable body composition and reduced BMD, which may imply an increased risk of cardiometabolic disease and osteoporosis later in life. Therefore, this strongly suggest that efforts should focus on encouraging EP/ELBW-born individuals to participation in PA.

The World Health Organization has created a model to describe the interaction between functioning, disability, and health [330]. This conceptual model can be used to describe known factors affecting PA in EP/ELBW-born subjects and help target interventions to promote PA participation according to individuals' preferences (Figure 9).

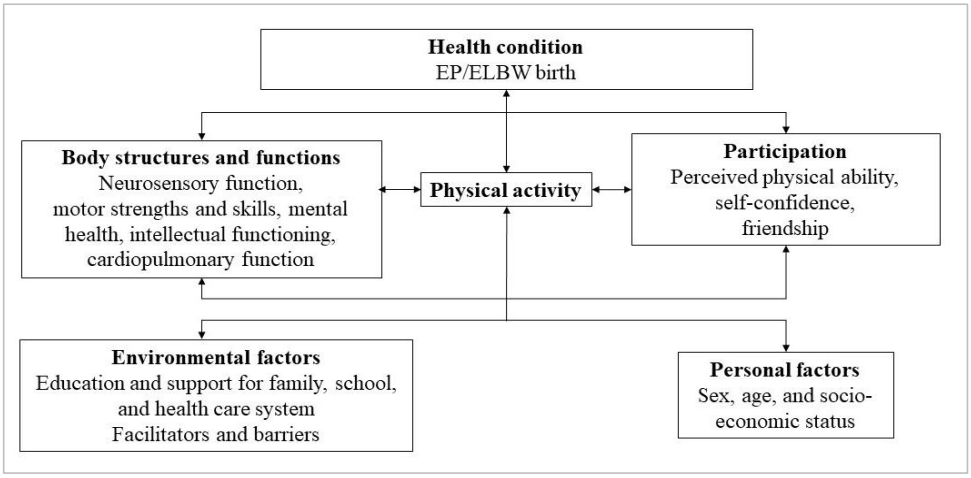

Figure 9 Model of interactions between physical activity, functioning, disability, and health in EP/ELBW-born subjects**.** Modified from the World Health Organization's *International Classification of Functioning, Disability and Health* (ICF) [330].

The clinical implication of the modest deficit in peak VO_2 seen in the EP/ELBW-born population is not clear. The HUNT fitness study examined more than 4600 healthy adults aged 20–90 years and observed that in both genders, each 5 ml/kg/min reduction in peak VO_2 corresponded to approximately 50% higher prevalence of a cluster of conventional cardiovascular risk factors. A peak VO_2 of 44 ml/kg/min in men and that of 35 ml/kg/min in women were suggested to represent the thresholds for cardiovascular risk [190]. Given an age-related decline in peak VO_2 observed in the general population, a deficit in young EP/ELBW-born adults of 5 ml/kg/min may be relevant in the long term.

Reports of negative postoperative outcomes have contributed to a decline in open PDA surgery rates over the last decade [331]. New catheter-based procedures for PDA closure have become an option also for EP/ELBW infants [332]. Outcomes after open PDA surgery in the preterm-born population may therefore become less relevant. However, there are generations of preterm-born subjects with a history of neonatal open PDA surgery who are now growing into adulthood. Clinicians caring for these individuals

need to be aware of long-term sequelae and outcomes associated with PDA-surgery and LVCP to ensure proper follow-up.

8.2.8 General study limitations (Papers I, II and III)

Observational studies can only find associations between exposure and outcome and cannot provide evidence on causes and effects. Study findings presented in this thesis need to be confirmed by others. Of note, the regional birth cohort was small, although comparable to birth cohorts in other follow-up studies on EP/ELBW populations.

Power calculations were not performed for the hypotheses presented in Papers I, II and III. Small sample sizes and large within-group variations resulted in wide CIs for several outcomes, e.g. when comparing the groups with and without LVCP, resulting in inconclusive results. It is possible that some results were incorrectly reported as insignificant due to the small study sample size (type II error). Although the level of statistical significance was set at $p \leq 0.01$ as an adjustment for multiple comparisons in the study discussed in Paper I, type 1 error, i.e., incorrectly reporting findings as statistically significant, might have occurred, given the overall high number of analyses in the study.

Retaining subjects' continued participation in cohort studies comprising multiple follow-up waves is challenging and may result in missing data. In the present studies, the issue of missing data was not addressed, apart from comparing participating and non-participating groups in terms of background characteristics.

8.3 Methodological considerations and discussion of main results in Paper IV

Measuring the reproducibility of a biological variable is challenging, as both within-subject variation and errors introduced from measurement methods will affect the result. In the case of maximal exercise testing, test personnel may also introduce errors because of varying personal skills in how to guide and encourage the test subject to continue performing the test until maximal exertion is achieved.

8.3.1 Study design

The key strength of this method comparison study was its randomised cross-over design. To minimise within-subject variation, only healthy subjects familiar with high-intensity exercise were included. Furthermore, similar pretest preparations were requested before both CPET and the CLE test. The two tests were performed 2–4 days apart (maximal limit of 14 days) to avoid changes in 'state of fitness', although diurnal variation was not accounted for as both tests were not routinely scheduled at the same time of the day. The test personnel consisted of only three people, providing instructions and encouragement to test subjects in a similar manner.

The measure of peak VO_2 may be influenced by a learning effect [191] and test results obtained from subjects familiar with CPET may differ from those who are tested for the first time. To avoid a possible bias introduced by a learning effect during the study, both ordinary CPET and CPET with CLE setup were performed in a randomised order. Information on previous experiences with exercise testing, flexible laryngoscopy, or CLE testing was not reported by participants. According to the test laboratory records, six of the participants had undergone ordinary CPET prior to the study. Because the distance to the nearest cardiopulmonary laboratory capable of performing the CLE test was 600 km, it was presumed that none of the participants had undergone a CLE test prior to this study. Thus, it can be assumed that the results reported in Paper IV were unlikely to be biased by previous test experiences.

8.3.2 Statistical considerations and interpretation of results

The results of the agreement analysis, by the method described by Bland and Altman, was the most important outcome in this method comparison study [333]. First, the average systematic bias of one method relative to another was estimated by determining the mean difference. A significant difference was seen in the completed distance on the treadmill, which was 49 metres longer in CPET compared to the CLE test. One potential explanation for this finding could be the extra weight and higher work of breathing with one nostril occluded by the laryngoscope during the CLE test. A systematic bias was not found for the other parameters.

Second, the likely agreement between the two methods for a given individual was estimated by the LoA (mean difference ±1.96 SD of the difference). If the range covered by the LoA is considered clinically not important, the two methods may be used interchangeably. For peak VO_2, LoA of ±3.5 ml/kg/min was beforehand considered to be an acceptable outcome, although a wider range of LoA would often be satisfactory in clinical settings.

The study revealed an agreement (95% LoA) between CPET and the CLE test for peak VO_2 of 0.2 ±3.7 ml/kg/min. This was a marginally wider range of the LoA than was considered clinically acceptable a priori, yet still useful in a clinical setting. The LoA for VE was rather wide (2.6 l ±24 l, corresponding to ±15% of the mean value). Similarly wide LoA for peak VE has been found on repeated CPET in healthy adults using a cycle ergometer [334]. Based on the results presented in Paper IV, identification of ventilatory limitation to exercise should not be based solely on measures of peak VE and subsequent calculation of breathing reserve.

The CoV shows the extent of variability of a measurement in relation to the mean and is an expression of precision and reproducibility. The present study showed that the CoV for peak VO_2 and other variables of gas exchange measured with standard CPET and the CLE test, were within the range of previously reported CoVs in studies assessing repeated CPET [191,334]. In studies examining healthy subjects, the CoV for peak VO_2, VE, HR, and RER in repeat CPET were 4.9–5.1%, 7.4–9.5%, 1.8–2.9% and

3.9–4.2%, respectively [197,334,335], compared to the present study with respective values of 2.6%, 6.2%, 2.5% and 3.1%. Thus, the reproducibility of CPET with and without CLE setup was within the expected range for repeat CPETs, and the added laryngoscope did not seem to introduce increased variability.

The test–retest reliability of the variables of gas exchange obtained by CPET and the CLE test was reported as the ICC. Excellent reliability was obtained for peak VO_2 and VE (ICC >0.9) and moderate or good reliability for RER, RR, and HR (ICC in the range of 0.5–0.7). The ICC represents a ratio of between-subject variability to between-subject variability plus errors. Hence, the magnitude of the ICC depends on the data variability [336]. Low between-subject variability, as in the case of RER, will results in lower ICC, even if measurement errors are small. Furthermore, comparing the ICC between studies involving groups with different heterogeneity should be performed with caution and was therefore not carried out.

8.3.3 Study limitations

Potential candidates for CPET and the CLE tests are subjects complaining of shortness of breath or breathing difficulties during physical exertion. In the present study, information on perceived dyspnoea was not obtained; hence, assessing how the CLE test, compared to regular CPET, impacted perceived dyspnoea among participants was not possible—which could be considered a study limitation. Although assessment of perceived dyspnoea was not a study aim, this information would be valuable.

8.3.4 Conclusions and clinical implications of study findings (Paper IV)

In individuals who are used to regular aerobic exercising, peak VO_2 and most of the other parameters obtained from the CLE test can be used interchangeably with data obtained from ordinary CPET. Thus, CPET with CLE setup would be preferable when assessing patients with unexplained exertional breathing problems. Further research is needed to determine agreement in measurement of ergospirometry variables obtained with and without added CLE test in subjects less familiar with endurance exercise training and, if needed, also to determine measures to prevent disagreement.

9. CONCLUSIONS

The overarching conclusion of the studies presented in this thesis was that EP/ELBW-born children, as well as young adults, were less physically active than TB controls, and young EP/ELBW-born adults had poorer exercise capacity compared to TB controls. Based on the study aims and RQs (Section 4), the key study conclusions can be summarised as follows:

RQ1: EP/ELBW-born schoolchildren and young adults born in Norway in the period from 1999 to 2000 were less physically active than TB controls. Based on parental reports, these children participated less frequently in PA, and were less vigorous and had lower endurance and poorer proficiency during PA than TB controls. The group of EP/ELBW-born children with NDD had poorer outcomes in all these aspects of PA compared to healthy EP/ELBW-born children.

RQ2: EP/ELBW-born children had lower muscle mass and BMD, and showed signs of increased truncal fat distribution, compared to TB children; however, no difference in %BF and FM was noted between the groups. The association between PA frequency, and BMD and muscle mass was weaker in EP/ELBW-born children compared to TB children.

RQ3: Healthy 5-year-old EP/ELBW-born children with problems such as impaired motor coordination, behavioural problems, and borderline intellectual functioning were at increased risk of being clumsy and less vigorous, and of having reduced endurance and poor proficiency when engaging in PA at age 11 years.

RQ4: Young EP/ELBW-born adults who underwent neonatal surgical PDA closure had a high prevalence of LVCP, which was associated with voice symptoms and laryngeal obstruction during exercise, but not with reduced lung function or poorer exercise capacity.

RQ5: Young EP/ELBW-born adults who underwent neonatal surgical PDA closure had reduced lung function, compared to EP/ELBW-born young adults not exposed to PDA surgery, as well as compared to TB controls. Overall, exercise capacity was lower in young EP/ELBW-born adults, compared to TB controls; however, this was not associated with a history of previous PDA surgery.

RQ6: In healthy young and middle-aged individuals familiar with exercise training, peak VO_2 and most other parameters of gas exchange measured by the CLE test may be used interchangeably with measurements from a standard CPET.

10. FUTURE PERSPECTIVES

In the preterm-born population, the effects of PA on future health outcomes should be further explored. Preferably, mapping health challenges should lead to intervention studies to improve outcomes. Based on the study findings presented in this thesis, several recommendations for future studies are suggested.

Longitudinal follow-up studies on EP and ELBW cohorts born in the post-surfactant era should aim to determine the association between PA and exercise capacity, and the effects of PA on long-term health outcomes in these populations. Moreover, studies should aim to investigate potential differences in outcomes related to sex, to identify those who would benefit from closer follow-up. A standardised method of self-assessment with use of questionnaires with established and validated psychometric properties, in combination with accelerometry, would be preferable to examine differences between cohorts, trajectories of PA over time, and the effects of PA on health outcomes.

Furthermore, intervention studies should be designed to determine how to improve PA and investigate the effects of PA on BMD, skeletal muscle mass and exercise capacity in EP/ELBW-born children and adults.

In subjects complaining of exertional dyspnea, CPET with added continuous laryngoscopy (the CLE test) may be used to assess laryngeal movement in addition to providing a comprehensive assessment of the cardiorespiratory response to exercise. Further research is needed to determine agreement in variables of gas exchange and perceived dyspnea obtained by CPET with and without added CLE setup, in subjects with low levels of PA or who are unfamiliar with endurance exercise training.

Table 2 Questionnaire-based assessment for physical activity in adults*

Study	BW/GA (g/wk)	Year of birth	Age (y)	Preterm (*n*)	TB (*n*)	Outcome PA Preterm-born vs TB
Saigal 2007, **Canada**[201]	<1000 g	1977-82	23	149	133	**Less PA** Regular participation in sports/strenuous activities: 38% vs 59% (p <0.001)
Morrison 2020, **Canada**[207]	<1000 g	1977-82	30-34	49	39	**No difference** In reported time spent performing light, moderate or vigorous PA
Kajantie 2010, **Finland**[16]	<1500 g	1978-85	18-27	163	188	**Less PA** Exercise to maintain physical condition for ≥ 3 times/wk: 22% vs 41% Lower intensity and shorter duration of PA sessions (p <0.001)
Caskey 2016, **UK**[286]	<1500 g	1978-93	19-33	49	25	**Less PA** PA at least 2-3 hours/wk: 24% vs 64% (p <0.05)
Rogers 2005, **Canada**[281]	≤800 g	1981-86	16-20	53	31	**Less PA** PA ≥ 3 times/wk: ~25% vs ~75% (p <0.001)
Clemm 2014, **Norway**[287]	<1000 g/ ≤28 wk	1982-85	25	34	33	**No difference** PA ≥2-3 hours/wk: 47% vs 59%
Vrijlandt 2006, **Netherland**[15]	<1500 g/ <32 wk	1983	19-20	42	48	**Less PA** PA mean (SD) hours/wk: 1.9 (2) vs 2.9 (2) (p = 0.04)
Yang 2021, **New Zealand**[337]	<1500 g	1986	26-30	202	93	**Less PA** Mean moderate/vigorous exercise days/wk: 2.9 vs 3.7 (p = 0.02) Regular exercise 36% vs 48 % (p = 0.03)
Haraldsdottir 2019, **USA**[163]	<1500 g	1989-91	25-27	12	16	**No difference** Similar estimates for metabolic equivalent min/week
Roberts 2013 **Australia**[338]	<1000 g/ <28 wk	1991-92	18	192	146	**Less PA** Regular PA past 6 months: 40% vs 56 % (p <0.01)
Clemm 2015, **Norway** [339]	<1000 g/ ≤28 wk	1991-92	18	26	22	**Less PA** PA hours/wk: ~ 1 hour/wk less for preterm (p <0.05) Times/wk: No difference

* Overview over studies comparing physical activity between EP/ELBW- or VP/VLBW-born adults and TB controls.
BW, birthweight; ELBW, extremely low birthweight; EP, extremely preterm; GA, gestational age; PA, physical activity; VLBW, very low birthweight; VP: very preterm; SD, standard deviation; TB, term-born; wk, week; y, years.

Table 3 Questionnaire-based assessment for physical activity in children and youths*

Study	BW/GA (g/wk)	Year of birth	Age (y)	Preterm (*n*)	TB (*n*)	Outcome PA Preterm-born vs TB
Kilbride 2003, **USA**[13]	<801 g	1983-89	9-15	50	25	**Less PA** Occasionally active or inactive: 18% vs 0% (p = 0.036)
Kriemler 2005, **Canada**[162]	<1500 g / <30 wk	1988-90	5-7	17 (BPD+) 14 (BPD–)	24	**No difference** PA hours/wk (SD): 8.4 (6.4) (BPD+) and 10.0 (4.0) (BPD–) vs 11.0 (8.4) (TB)
Joshi 2013, **UK**[340]	<32 wk	Not reported	8-12	29 (BPD+) 33 (BPD–)	30	**Less PA for BPD group** PA hours/wk, median (range): 2.0 (0-24) (BPD+) and 3.0 (0-10) (BPD–) vs 3.5 (0-24) (TB) (p <0.05)
Prenzel 2020, **Germany**[217]	<1500 g	1994-02	11-12	42 (BPD+)	42	**No difference** Preterm more difficulties in PA, shorter duration of PA without a break compared to TB
MacLean 2016, **Canada**[216]	≤28 wk	1997-04	8-12	47 (BPD+) 53 (BPD no/mild)	64	**Less PA** Spending "more than average" time in any sport/PA: 32% (BPD+) and 51% (BPD no/mild) vs 63% (TB) (p = 0.04)
Novais 2012, **France**[341]	<1500 g	1998-00	8-10	19	20	**No difference** PA mean (range) hours/wk: 2.0 (1.0-2.9) vs 1.0 (0.1-2.0)
Engan 2020, **Norway**[17]	<1000 g/ <28 wk	1999-00	11	231	57	**Less PA** PA ≤1 day/wk: 31% vs 14% (p = 0.02)
Spiegler 2019, **UK**[205]	<32 w	2000-02	5+7+ 11+14	422	36994	**Less PA at 14 y only** Daily ≥ 60 min MVPA: 11% vs 19%
Haraldsdottir 2018, **USA** [342]	<1500 g/ <32 wk	2003-04	12-14	21	20	**No difference** Similar score obtained from PA questionnaire
Tsopanoglou 2014, **Brazil**[161]	<1500 g	2001-06	6-9	36	34	**No difference** PA mean (SD) hours/wk: mean (SD) 3.4 (4.0) vs 3.1 (3.7)
Tsopanoglou 2020, **Brazil**[280]	<1500 g	2004-09	6-9	34	32	**No difference** PA mean (SD) hours/wk: 3.3 (1.4) vs 3.8 (1.5)

* Overview over studies comparing physical activity between EP/ELBW- or VP/VLBW-born children and youths and TB controls. BPD, bronchopulmonary dysplasia; BW, birthweight; ELBW, extremely low birthweight; EP, extremely preterm; GA, gestational age; MVPA, moderate to vigorous physical activity; PA, physical activity; VLBW, very low birthweight; VP: very preterm; SD, standard deviation; TB, term-born; wk, week; y, years.

Table 4 Physical activity determined by accelerometry*

Study	BW/GA (g/wk)	Year of birth	Age (y)	Preterm (*n*)	TB (*n*)	Outcome PA Preterm-born vs TB
			Adults			
Morrison 2020, **Canada**[207]	<1000 g	1977-82	30-34	49	39	**No difference**
Kaseva 2015, **Finland**[208]	<1500 g	1978-85	24-25	57	47	**No difference**
Landry 2016, **Canada**[209]	< 32 wk	1987-93	21-22	20 (BPD+)	24	**Less PA** PA duration: ~40 min less per day (p = 0.05) No difference in moderate PA
			Children			
Lowe 2015, **UK**[203]	25-32 wk	1991-92	11+15	48+ 24	5025+1829	**No difference**
Welsh 2010, **UK**[204]	<750 g/ <25 wk	1995	10-11	31	30	**No difference**
Ruf 2019, **Germany**[283]	<1500 g/ <32 wk	1997-01	8-12	21	13	**Less PA** MVPA: ~15 min vs ~35 min per day (p <0.001)
Lowe 2016, **UK**[282]	25-32 wk	2000-02	7	79	5949	**Less PA** MVPA: ~1 hour/wk less for preterm boys (p = 0.06)
Spiegler 2019, **UK**[205]	<32 wk	2000-02	14	46	3729	**No difference**
Svedenkrans 2020, **Sweden**[206]	< 27 wk	2004-07	6-7	71	87	**Less PA** MVPA/day: 25 min less for preterm boys (p = 0.003)
FitzGerald 2021 **Australia**[284]	<30 wk	2011-13	4-6	96	106	**Less PA** Non-stationary activity: ~40 min/day less for preterm children (p <0.001)

* Overview over studies comparing physical activity between EP/ELBW- or VP/VLBW-born subjects and TB controls.
BPD, bronchopulmonary dysplasia; BW, birthweight; ELBW, extremely low birthweight; EP, extremely preterm; GA, gestational age; MVPA, moderate to vigorous physical activity; PA, physical activity; VLBW, very low birthweight; VP: very preterm; SD, standard deviation; TB, term-born; wk, week; y, years.

Table 5 Exercise capacity in adults

Study	BW/GA g/wk	Year of birth	Age (y)	Method	Preterm (*n*)	TB (*n*)	Outcome VO_2 (ml/kg/min) Preterm-born vs TB
Lovering 2013, **USA**[343]	≤32 wk	-	18-31	Bicycle	12 (BPD+) 12 (BPD–)	14	**Deficit in peak VO_2** Mean (SE) 40.6 (9.4) (BPD–) and 40.7 (14.3) (BPD+) vs 48.8 (7.6) (TB) (p >0.05)
Caskey 2016, **UK**[286]	<1500 g	1978-93	19-33	Treadmill	22 (BPD+) 20 (BPD–)	24	**Lower peak VO_2** Mean (SD) 35.6 (7.5) (BPD+) and 39.3(8.8) (BPD–) vs 45.2 (11.3) (TB) (p <0.05) Percentage of % predicted VO2: Mean (SD) 82 (14)% (BPD+) and 92 (17)% (BPD–) vs 108 (23)% (TB) (p <0.05)
Clemm 2012, **Norway**[14]	<1000 g/ ≤28 wk	1982-85	17-20	Treadmill	40	40	**Deficit in peak VO_2** Mean (95% CI) 47.1 (44.4, 49.9) vs 49.9 (46.6, 53.3) (p = 0.12) Peak VO_2 positively correlated with PA
Clemm 2014, **Norway**[287]	<1000 g/ ≤28 wk	1982-85	25	Treadmill	34	33	**Deficit in peak VO_2** Mean (95% CI) 40.7 (37.9, 43.5) vs 44.2 (41.0, 47.4) (p = 0.055) Peak VO_2 positively correlated with PA
Vrijlandt 2006, **Netherlands**[15]	<1500 g/ <32 wk	1983	18-22	Bicycle	41	47	**Deficit in peak VO_2** Mean (SD) 35.3 (6.9) vs 37.4 (6.3) (p = 0.14) Percentage of predicted peak VO_2: Mean (SD) 93 (10)% vs 105 (20)% (p < 0.001) 15% reduced max workload (watt) Impaired physical fitness. Higher rest metabolism?

* Overview of studies comparing peak VO_2 in EP/ELBW- or VP/VLBW-born adults and TB controls (only studies assessing peak VO_2 by maximal CPET using treadmill or bicycle protocols). BPD, bronchopulmonary dysplasia; BW, birthweight; CI, confidence interval; ELBW, extremely low birthweight; EP, extremely preterm; GA, gestational age; PA, physical activity; VLBW, very low birthweight; VO_2, oxygen consumption; VP: very preterm; SE, standard error; SD, standard deviation; SGA, small for gestational age; TB, term-born; wk, week; y, years.

Table 5 *(continued)*

Study	BW/GA g/wk	Year of birth	Age (y)	Method	Preterm (*n*)	TB (*n*)	Outcome VO_2 (ml/kg/min) Preterm-born vs TB
Yang 2021, **New Zealand**[337]	<1500 g	1986	26-30	Bicycle	202	93	**Lower peak VO_2** Mean (95% CI) difference VO_2 % predicted: -9.3% (-14.0, -4.6) (p <0.001)
Evensen 2009, **Norway**[344]	<1500 g/ 24-35 wk	1986-88	18	Treadmill	32	51	**No difference in peak VO_2** Mean (SE) 48.8 (1.4) vs 48.5 (1.1) (p >0.05) Preterm SGA worse outcome; more body fat, less favourable fat distribution or higher proportions of smokers
Haraldsdottir 2019, **USA**[163]	<1500 g	1989-91	25-27	Bicycle	12	16	**Lower peak VO_2** Mean (SD) 34.9 (9.3) vs 45.8 (8.7) (p = 0.003) Male preterm worse outcome
Farrell 2015, **USA**[345]	<1500 g	1989-91	21-23	Bicycle	14	16	**No difference in peak VO_2** Mean (SE) 39.5(1.7) vs. 38.9 (1.6) (p >0.05) Lower pulmonary gas exchange efficiency in some preterm
Clemm 2015, **Norway**[339]	<1000 g/ ≤28 wk	1991-92	18	Treadmill	26	20	**No difference in peak VO_2** Mean (95% CI) 44.1(40.7, 47.5) vs 45.3(41.3, 49.3) (p = 0.42) without minor disabilities Preterm with minor disabilities (n= 6) worse outcome: Mean difference (95% CI) 36.3 (29.5, 43.1) Male preterm worse outcome
Engan 2021, **Norway**[220]	<1000 g/ <28 wk	1999-2000	18-20	Treadmill	55	36	**Lower peak VO_2** Mean (95% CI) difference: -4.9 (-8.0, -1.8) (p = 0.002)

Table 6 Exercise capacity in children aged < 18 years*

Study	BW/GA g/wk	Year of birth	Age (y)	Method	Preterm (*n*)	TB (*n*)	Outcome VO_2 (ml/kg/min) Preterm-born vs TB
Bader 1987, **USA**[346]	<32 wk	1973-79	9-11	Treadmill	10	8	**Deficit in peak VO_2** Mean (SEM) 39.1(3.7) vs 43.0(3.8) (p >0.05) Pulmonary limitation BPD
Baraldi 1991, **USA**[347]	<1500 g/ <32 wk	1973-79	8-12	Treadmill	15	26	**No difference in peak VO_2** Mean (SD) 42.9 (9.1) vs 42.7 (9.9)
Jacob 1997, **Canada**[218]	<1500 g/ <32 wk	1981-87	9-13	Bicycle	30 (BPD+) 30 (BPD–)	13	**No difference in peak VO_2** Mean (SD) 36.1 (7.0) (BPD+) and 36.7 (9.2) (BPD–) vs 37.9 (5.3) (TB) BPD used more ventilatory reserve
Santuz 1995, **Italy**[348]	<1400 g/ <30 wk	1981-87	6-12	Treadmill	12	16	**Lower peak VO_2** Mean (SD) 25.2 (10.3) vs 37.1 (10.4) (p < 0.01) Deficit in gas exchange
Kilbride 2003, **USA**[13]	<801 g	1983-89	11	Treadmill	47	25	**Lower peak VO_2** Mean (SD) 31.2 (6.3) vs 38.5 (5.2) (p < 0.001) Low level of fitness, unrecognised physiologic limitation?
Gross 1998, **USA**[349]	<32 wk	1985-86	7	Treadmill	43 (BPD+) 53 (BPD–)	108	**No difference in peak VO_2** Mean (SD) 41.1 (7.5) (BPD+) and 43.7 (5.4) (BPD–) vs 43.2 (8.6) (TB)
Heberstreit 2003, **Germany**[350]	<1500 g/ <32 wk	1985-89	6-12	Bicycle	32	21	**No difference in peak VO_2** Mean 43.9 (small HC) and 45.6 (normal HC) vs 44.0 (TB) Small head circumference (HC) associated with increased oxygen demand during exercise
Parat 1995, **France**[351]	<1900 g/ <32 wk	1986	7.5	Bicycle	6 (BPD+) 5 (BPD–)	5	**No difference in peak VO_2** Mean (SD) 37 (3.4) (BPD+) and 40 (9) (BPD–) vs 41 (9) (TB)

* Overview of studies comparing peak VO_2 in EP/ELBW- or VP/VLBW-born children and youths and TB controls (only studies assessing peak VO_2 by 20-metre shuttle run test or maximal CPET using treadmill or bicycle protocols). BPD, bronchopulmonary dysplasia; BW, birthweight; CI, confidence interval; ELBW, extremely low birthweight; EP, extremely preterm; GA, gestational age; HC, head circumference; PA, physical activity; VLBW, very low birthweight; VO_2, oxygen consumption; VP: very preterm; SEM, standard error of mean; SD, standard deviation; SGA, small for gestational age; TB, term-born; wk, week; y, years.

Table 6 *(continued)*

Study	BW/GA g/wk	Year of birth	Age (y)	Method	Preterm (*n*)	TB (*n*)	Outcome VO_2 (ml/kg/min) Preterm-born vs TB
Pianosi 2000, **Canada**[212]	<1200 g/ <28 wk	1986-87	8-9	Bicycle	17 (BPD+) 15 (BPD–)	15	**Lower peak VO_2** Mean (SD) 40 (6) (BPD+) and 41 (8) (BPD–) vs 46 (8) (TB) ($p < 0.05$) Lower lean body mass; higher respiratory rate.
Kriemler 2005, **Canada**[162]	<1500 g /30 wk	1988-90	5-7	Bicycle	17 (BPD+) 14 (BPD–)	24	**No difference in peak VO_2** Mean (SEM) 32.0 (4.9) (BPD+) and 29.0 (2.6) (BPD-) vs 32.8 (8.3) (TB) Different ventilatory pattern. Higher oxygen cost per power output for those with chronic lung disease.
Clemm, 2012, **Norway**[14]	<1000 g/ ≤28 wk	1991-92	10-11	Treadmill	35	35	**No difference in peak VO_2** Mean (95% CI) 43.5 (40.7, 46.3) vs 45.7 (43.3, 48.0)
Burns 2009, **Australia**[214]	<1000 g/ <29 wk	1992-94	11-13	20m shuttle run	55	54	**Lower estimated peak VO_2** Mean (SD) 42.1 (4.9) vs 46.1 (5.8) ($p < 0.001$) Poor motor coordination
Smith 2008, **Australia**[352]	<1000 g/ 32 wk	1992-94	10-11	20m shuttle run	125	34	**Lower estimated peak VO_2** Mean (SD) 41.6 (2.8) vs 45.5 ($p < 0.001$) Deconditioning and lack of fitness
Danks 2013, **Australia**[294]	<1000 g	1992-94	11-13	20m shuttle run	48	55	**Lower estimated peak VO_2** Mean (SD) 42.8 (4.8) vs 46.1 (5.8) ($p = 0.02$) Poor general competence
Prenzel 2020, **Germany**[217]	<1500 g	1994-02	11-12	Bicycle	42 (BPD+)	42	**No difference in peak VO_2** Mean (SD) 41.1 (8.1) vs 41.7 (8.3) Preterm with BPD lower max workload
Ruf 2019, **Germany**[283]	<1500 g/ <32 wk	1997-01	8-12	Bicycle	9 (BPD+) 13 (BPD–)	15	**Lower peak VO_2 associated with BPD** Peak VO_2% (SD) 83 (11)% (BPD+) and 91 (8)% (BPD–) vs 94 (9)% (TB) ($p = 0.02$) Impaired exercise tolerance because of constraints in lung function

Table 6 *(continued)*

Study	BW/GA g/wk	Year of birth	Age (y)	Method	Preterm (*n*)	TB (*n*)	Outcome VO_2 (ml/kg/min) Preterm-born vs TB
O'Dea 2018, **Australia**[353]	≤32 wk	1997-03	9-12	Bicycle	68 (BPD+) 55 (BPD–)	48	**No difference in peak VO_2** Mean (SD) 47.7 (BPD+) and 46.1 (BPD–) vs 48.1 (TB) BPD rapid shallow breathing and expiratory flow limitation
Welsh 2010, **UK**[204]	<750 g/ <25 wk	1995	10-11	Bicycle	31	30	**Lower peak VO_2** Mean difference (95% CI) -253 ml/min (-359, -147) (p <0.001) Poor growth and development
MacLean 2016, **Canada**[216]	≤28 wk	1997-04	8-12	Bicycle	43 (BPD+) 51 (BPD no/mild)	65	**Lower peak VO_2 for moderate/severe BPD vs TB** Mean (SE) 36.9 (10.7) (BPD+) and 44.6 (9.2) (BPD no/mild) vs 42.6 (9.6) (TB) Expiratory flow limitation
Joshi 2013, **UK**[340]	<32 wk	Not reported	8-12	Bicycle	24 (BPD+) 26 (BPD–)	62	**No difference in peak VO_2** Mean (95% CI) 35.4 (33, 38) (BPD+) and 35.0(32, 38) (BPD–) vs 31.1(28, 35) (TB) Those with chronic lung disease used more of their ventilator reserve.
Haraldsdottir 2018, **USA**[342]	<1500 g/ <32 wk	2003-04	12-14	Bicycle	21	20	**Deficit in peak VO_2** Mean (SD) 43.3 (6.9) vs 48.3 (11.0) (p = 0.47) Preterm lower max workload and shorter time to exhaustion
Tsopanoglou 2020, **Brazil**[280]	<1500 g	2004-09	6-9	Treadmill	34	32	**No difference in peak VO_2** Mean (SD) 40.4 (6.5) vs 39.5 (6.4)

Note: The studies listed in tables 2-6 were identified using a search strategy in PubMed including the following search words 'preterm', 'prematurity', 'exercise capacity', 'aerobic capacity', 'physical activity', 'physical fitness', 'exercise', 'leisure time exercise'. Furthermore, the references list of included papers were reviewed.

Errata

Paper I: 'Participants' under 'RESULTS' p. 2, '*Of 108 premature EP/ELBW children, 19 had died and 57 (29 males) consented to participate in the follow-up study'.* This statement is incorrect and should read: "*Of 106 premature EP/ELBW children, 18 had died and 57 (29 males) consented to participate in the follow-up study".* This error has minor and statistically insignificant implications for the results presented in Table 1 and does not affect the main results.

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12. Papers I, II, III and IV

Paper I

BMJ Paediatrics Open

Comparison of physical activity and body composition in a cohort of children born extremely preterm or with extremely low birth weight to matched term-born controls: a follow-up study

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ABSTRACT

Objectives To compare physical activity and body composition in a cohort of children born extremely preterm/extremely low birth weight (EP/ELBW) with term-born (TB) controls.

Methods A regional cohort of children born during 1999–2000 at gestational age <28 weeks or with birth weight <1000 g and their individually matched TB controls were examined in 2010–2011. Information on physical activity was obtained from parental questionnaires, and body composition was determined by anthropometry and dual X-ray absorptiometry.

Results Fifty-seven EP/ELBW and 57 TB controls were included at a mean age of 11.6 years. Compared with the TB children, the EP/ELBW-born children exercised less often (22% vs 44% exercised more than 3 days per week), had lower physical endurance and poorer proficiency in sports and play and were less vigorous during exercise ($p<0.05$). They also had lower values (mean; 95 % CI) for muscle mass (0.9; 0.3–1.5 kg), total bone mineral density z-score (0.30; 0.13–0.52 units) and fat mass ratio (0.14; 0.06–0.21 units). The association between physical activity and bone mineral and skeletal muscle mass accrual was significantly weaker for the EP/ELBW-born than the TB children.

Conclusions The EP/ELBW-born children were less physically active, had signs of an unfavourable body composition with less muscle mass and lower bone mineral density than the TB controls. The association between physical activity and the measures of body composition was weaker in the group of EP/ELBW-born children.

INTRODUCTION

Children born extremely preterm (EP; ie, before 28 weeks' gestation) or with extremely low birth weight (ELBW; ie, <1000 g) are considered to be at increased risk of cardiovascular disease and osteoporosis.[1] The reasons may be complex and probably include prenatal conditions like placental insufficiency and later exposures like infections, immobilisation and suboptimal nutrition.[2] Most of the skeletal muscle mass[3] and 80% of skeletal mineralization is normally acquired during the last trimester.[4] EP/ELBW-born individuals are deprived of these valuable intrauterine weeks, and they are usually shorter and lighter with lower lean body mass (LBM), lower bone mass and a higher percentage of total body fat (%BF) at term equivalent age than infants born at term.[5–7] It is uncertain to what extent these differences track into later life and how nutrition and physical activity (PA) modify the anthropometry and body composition in children born EP/ELBW.[8 9] However, suboptimal bone and muscle mass may persist and lead to compromised skeletal and muscle health.[10–12]

PA is associated with numerous health benefits including reduced risk of cardiovascular disease and osteoporosis through improved insulin sensitivity, reduced blood pressure, enhanced endothelial function and increased bone mineralisation.[13 14] There is inconsistent evidence on whether children and young adults born EP/ELBW differ from children born at term regarding PA.[15–18] Moreover, we do not know if PA has the same beneficial effects in individuals born EP/ELBW as in those born at term. Therefore, the purpose of this study was to compare exercise habits and body composition in schoolchildren born EP/ELBW with term-born children and to assess the association between PA and body composition in the two groups.

METHODS

Participants

This follow-up cohort study in a high-income country included 57 children born EP

(gestational age (GA) <28 weeks) or with ELBW (<1000 g) in the Western Norway Regional Health Authority during 1999–2000 participating in the Project Extreme Prematurity, which is a part of the WestPaed Research Group. The EP/ELBW children were included at birth and later examined at 2 and 5 years of age before this study was performed in 2010–2011. Neonatal care had been provided at one of two regional neonatal intensive care units. Medical data were obtained from clinical examinations and hospital records. Using information from birth protocols at the maternity wards, the next born individuals of the same sex, born at term (TB, GA >37 weeks) with a birth weight (BW) above the lower 10th percentile of Norwegian children (>3.0 kg)[19] at the same maternity ward as the participating EP/ELBW-born index case were invited as controls in 2010. If the parent of the first invited term-born individual declined participation, the next was invited and so on until one TB control was recruited for each participating preterm born index child. One average 1.6 controls had to be invited to recruit a full 1:1 TB control group.

PA questionnaires

Exercise habits were reported on questionnaires by the parents. A validated question from the *WHO Health Behaviour in Schoolchildren Survey* was used to determine the frequency of leisure time PA: *apart from at school, how often do you usually exercise so much that you get out of breath or sweat?*[20]

Anthropometry

Height, weight, subscapular and triceps skinfolds and waist circumference were measured. Subscapular to triceps skinfold ratio (STR) and waist-to-height ratio (WHtR) were calculated as estimates of truncal fat mass (FM). Z-scores for BW and anthropometric measures were calculated with reference to Norwegian growth curves.[19 21 22] Small for gestational age (SGA) was defined as a BW <10th percentile for GA.[19]

Dual-energy X-ray absorptiometry (DXA)

DXA is a validated method to determine body composition.[23] The participants were examined at two different centres of rheumatology on a Lunar Prodigy and Lunar Prodigy Advanced DXA scan (GE Medical systems Lunar, Madison Wsconsin, USA). Daily calibration with a local phantom provided by the manufacturer was performed at the two DXA centres, and the preterm and their matched TB controls were examined at the same centre according to geographic affiliation.

Whole-body less head and regional body composition were measured, and bone mineral density (BMD) z-scores were calculated using sex and age specific paediatric reference standards provided by Lunar Prodigy enCORE2009 software version 13.20.033.[23]

Data on bone mineral content (BMC) (total BMD, lumbar spine BMD (lumbar vertebra 1–4) and left and right total hip BMD (BMDth)), fat compartments (total FM, %BF, FM ratio ((arms+legs FM)/truncal FM) and fat mass index (FMI: FM normalised for height^2)) and skeletal muscle mass (LBM, appendicular lean mass (ALM), ALM index (ALMI: ALM/height^2) and LBM index (LBMI: LBM/height^2) were collected.

Blood samples

Blood for analyses of vitamin D (25-hydroxy vitamin D), oestradiol, testosterone, luteinising hormone and follicle-stimulating hormone was drawn at the consultation.

Puberty

The questionnaire contained a five-level question on puberty development, where parents were asked to compare their offspring to peers (delayed, somewhat delayed, similar, somewhat ahead or ahead of peers).

Statistics

Data are presented as means with SD or medians with ranges, as appropriate, or as mean group differences with 95% CIs based on the t-distribution with the appropriate df. To compare findings between the EP/ELBW and TB groups, a mixed linear model and Wilcoxon's signed-rank test were used. Independent sample t-tests were used to compare the SGA and the non-SGA preterm individuals. Leisure time exercise were adjusted for socioeconomic status defined by the maternal education (high education defined by minimum 3 years of college or university degree) and single parenthood. A mixed linear regression model adjusted the estimate of the body components for body size (height z-score and weight z-score), parental reported puberty and PA (days per week with exercise). Vitamin D level did not change the effect of EP/ELBW birth and was not included in the model. An interaction term was constructed to test differences between the EP/ELBW and TB groups regarding association between PA and body composition. P values have not been formally adjusted for multiple comparisons due to the complexity of the analyses and should be interpreted with caution. Accordingly, as a rule of thumb, we consider only p values <0.01 as statistically significant in the interpretation of the results. Analyses were performed using IBM SPSS statistics V.14.

Ethics

The mothers gave written informed consent.

Patient and public involvement

Patient representatives were involved in the study design of this and several other studies as part of the national follow-up study on EP/ELBW children.

RESULTS

Participants

Of 108 premature EP/ELBW children, 19 had died and 57 (29 males) consented to participate in the follow-up study. The participants needed more ventilator treatment but did not differ from those who declined on

Table 1 Characteristics of the 89 surviving EP/ELBW-born children and the 57 term-born children in the regional cohort of Western Norway health region in 1999–2000

	EP/ELBW born				
Characteristics	Assessed	Not assessed	P value*	Term born	P value†
Participants, n	57	32		57	
Female gender, n (%)	28 (49)	12 (38)	0.29	26 (46)	
Birth weight (g), mean (SD)	842 (175)	837 (142)	0.74	3700 (434)	
Gestational age (weeks), median (range)	27 (24–31)	27 (23-30)	0.68		
Small for gestational age, 0.10 percentile, n (%)	20 (35)	6 (19)	0.11		
Ventilator treatment, n (%)	51 (89)	21 (66)	0.01		
Days on ventilator, median (range)	5 (0–24)	2.5 (0–29)	0.01		
Bronchopulmonary dysplasia, n (%)	31 (54)	12 (38)	0.13		
Periventricular leucomalacia, n (%)	4 (7)	3 (9)	0.70		
Necrotising enterocolitis, n (%)	1 (2)	1 (3)	0.59		
Gastrostomy tube, n (%)	0 (0)	1 (3)	0.36		
Cerebral palsy at 5 years, n (%)	3 (5)	5 (16)	0.13		
Eating difficulties any time, n (%)	16 (28)	7 (22)	0.52		
Growth hormone treatment, n (%)	2 (4)	0 (0)	0.53		
Assessment at 11 years of age					
Reduced mobility, n (%)	2 (4)			0 (0)	0.16
Single parenthood, n (%)	13 (23)			6 (10)	0.052
Mother higher education‡, n (%)	31 (54)			35 (61)	0.85
Hearing impairment, n (%)	6 (11)			2 (4)	0.16
Visual impairment, n (%)	11 (19)			5 (9)	0.06
Inhaled corticosteroids, n (%)	3 (5)			3 (5)	0.66

The enrolled subjects were examined in 2010–2011.
*P value for differences between the participating extremely preterm/extremely low birth weight (EP/ELBW)-born children and the EP/ELBW-born children not participating. Independent sample t-test, Mann-Whitney test and χ^2 exact test as appropriate.
†P value for differences between the participation EP/ELBW-born and the TB control group. Wilcoxon signed-ranks test.
‡High education defined by minimum 3 years of college or university degree.
EP/ELBW, Extremely preterm/extremely low birth weight; TB, term born.

other characteristics (table 1). Seven of the EP/ELBW-born children declined DXA scanning, and three were excluded from the DXA analyses because they were of minority ethnicity. One of the included participants who underwent DXA scanning had mild cerebral palsy (CP) affecting one leg. One subject who was not scanned was excluded from analyses on PA because of deafness and hemiplegic CP. Among the TB controls, 57 (31 males) completed the questionnaires, 54 showed up for examinations and 49 underwent DXA scanning. Mean age (SD) at examination was 11.6 (0.7) years for both groups.

Exercise and participation in sports activities

Twenty-two per cent of the EP/ELBW-born and 44% of the TB children exercised more than 3 days/week, and the overall mean (95% CI) difference was 0.9 (0.2 to 1.6) days/week adjusted for socioeconomic status, p=0.009 There was no statistically significant gender difference.

More EP/ELBW-born than TB participants were reported to have lower physical endurance, poorer proficiency in sports and play and to be less vigorous during exercise, when compared with their peers (table 2).

Nearly 50% of the EP/ELBW and 72% of the TB participated in team sports. The difference was mainly explained by the EP/ELBW boys not participating at the same level as TB boys (52% vs 81%, p=0.005). The EP/ELBW-born children participated in PA together with family or friends more often than the TB children (75% vs 60%, p=0.050).

Body composition

The mean (95% CI) height was 4.6 (2.0 to 7.2) cm and the weight was 2.8 (0.3 to 5.8) kg lower in the EP/ELBW than the TB children. The z-score for height were lower in the EP/ELBW group but not statistically significant (p=0.04). The mean z-score for weight, BMI, waist circumference, subscapular skinfold, triceps skinfold and the z-scores for these measures did not differ significantly (table 3). The FM and %BF were similar, but the STR was 11% higher

Table 2 Comparing reported physical activity and participation in sports between the 56 EP/ELBW-born subjects and the 57 term-born age-matched and gender-matched controls in the Western Norway Health Region in 1999–2000 as part of the Project Extreme Prematurity

	EP/ELBW N=56 M=28, F=28		Term born N=57 M=31, F=26		
Physical activity	**N**	**(M/F)**	**N**	**(M/F)**	**P value***
Apart from at school, how often does your child usually exercise so much that it gets out of breath or sweats?					0.013
Daily	3	(2/1)	7	(6/1)	
4–6 times/week	9	(4/5)	18	(9/9)	
2–3 times/week	28	(15/13)	24	(13/11)	
1 time/week	9	(3/6)	6	(2/4)	
Less than one time/week	2	(1/1)	2	(1/1)	
Never	3	(2/1)	0		
Total	54		57		
At play and sports: how is the child's endurance compared with its average peers?					0.006
Similar	34	(17/17)	48	(25/23)	
Less	18	(9/9)	9	(6/3)	
Much less	3	(1/2)	0		
Total	55		57		
At play and sports: how vigorous is the child compared with its average peers?					0.001
More	6	(1/5)	16	(13/3)	
Similar	34	(20/14)	37	(15/22)	
Less	15	(6/9)	4	(3/1)	
Total	55		57		
How will you rate your child's proficiency in sports activities?					<0.001
Very high	6	(2/4)	11	(10/1)	
High	8	(2/6)	26	(13/13)	
Average	25	(15/10)	16	(6/10)	
Somewhat low	13	(7/6)	3	(2/1)	
Very low	2	(1/1)	0		
Total	54		56		
Does the child participate in					
Team sports	27	(14/13)	41	(25/16)	0.009
Sports club activities other than team sports	14	(6/8)	16	(10/6)	0.83
Physical activity alone or together with family/ friends	42	(21/21)	34	(18/16)	0.050

*Wilcoxon's signed-ranks test two tailed.
EP/ELBW, extremely preterm/extremely low birth weight; F, female; m, male.

(p=0.04) and the FM ratio was 11% lower (p=0.001) in the EP/ELBW than the TB children. After adjusting for size and reported puberty, the mean (95% CI) difference in STR was 0.09 (0.01 to 0.17) units (p=0.04), and the mean difference in FM ratio was 0.14 (0.06 to 0.21) units (p=0.001).

The EP/ELBW-born children had lower LBM, ALM, total BMD z-score and BMDth z-scores. The mean (95% CI) difference in ALM was 0.9 (0.3 to 1.5) kg (p=0.004), and the difference in total BMD z-score was 0.33 (0.13 to 0.52) units (p=0.001) after adjusting for size and puberty (table 4). The EP/ELBW children had close

Table 3 Comparing anthropometry and body composition between the 54 EP/ELBW children and their 54 age-matched and gender-matched term-born controls born year 1999–2000 in the Western Norway health region and examined in 2010–2011

	All					Female						Male					
	EP/ELBW (n=54) and TB (n=54)					EP/ELBW (n=26) and TB (n=25)						EP/ELBW (n=28) and TB (n=29)					
Variables, units	Mean	SD	Mean	SD	P value*	Mean	SD	Mean	SD	m	P value†	Mean	SD	Mean	SD	m	P value‡
Birth weight, g	842	175	3700	434	<0.001	842	168	3554	399	0	<0.001	840	184	3826	431	0	<0.001
Age at examination, years	11.4	0.6	11.7	0.7	<0.001	11.6	0.7	11.8	0.6	0	<0.001	11.5	0.7	11.7	0.7	0	0.005
Height, cm	146.7	8.0	151.5	8.4	0.001	146.6	7.2	149.5	8.7	0	0.19	146.9	8.7	153.3	7.9	0	<0.001
Height z-score	−0.41	1.06	0.01	1.11	0.04	−0.43	1.02	−0.30	1.28	0	0.68	−0.40	0.11	0.27	0.89	0	0.002
Weight, kg	38.5	8.3	41.3	8.6	0.07	37.5	7.2	41.1	9.58	0	0.17	39.4	9.3	41.3	7.85	0	0.28
Weight, z-score	−0.34	1.1	−0.13	1.1	0.32	−0.43	0.99	−0.19	1.20	0	0.47	−0.25	1.17	−0.08	0.96	0	0.53
BMI, kg/m^2	17.7	2.6	17.8	2.8	0.79	17.3	2.4	18.3	3.5	0	0.33	18.0	2.7	17.5	2.0	0	0.31
BMI, z-score	−0.19	1.06	−0.21	1.01	0.92	−0.38	1.09	−0.11	1.12	0	0.47	−0.02	1.01	−0.30	0.93	0	0.23
Waist circumference, mm	65.3	8.1	66.3	7.6	0.55	63.4	6.2	65.9	9.4	2	0.30	67.2	9.3	66.7	5.6	5	0.68
Waist circumference, z-score	0.23	1.02	0.29	1.04	0.74	−0.08	0.97	0.06	1.31	2	0.74	0.51	1.00	0.50	0.70	5	0.92
Subscapular fold, mm	8.7	4.0	8.6	4.3	0.87	8.0	3.1	9.5	4.9	5	0.23	9.3	4.5	7.7	3.5	5	0.13
Subscapular fold, z-score	0.12	1.18	0.01	1.20	0.53	0.00	1.24	0.30	1.06	5	0.39	0.23	1.15	−0.25	1.27	5	0.09
Triceps fold, mm	11.3	4.1	12.3	4.1	0.23	11.0	3.6	13.5	4.3	3	0.04	11.6	4.6	11.3	3.7	5	0.06
Triceps fold, z-score	−0.08	0.92	0.17	0.88	0.20	−0.12	0.82	0.40	0.81	3	0.03	−0.06	0.99	−0.03	0.91	5	0.95
WHtR	0.45	0.05	0.44	0.04	0.39	0.43	0.04	0.44	0.06	2	0.67	0.46	0.05	0.44	0.03	5	0.08
WHtR, z-score	0.48	0.92	0.34	0.97	0.42	0.13	0.87	0.22	1.24	2	0.87	0.81	0.85	0.44	0.66	5	0.10
STR	0.78	0.24	0.70	0.21	0.04	0.75	0.18	0.71	0.21	5	0.45	0.81	0.27	0.69	0.21	5	0.050
Fat mass, kg	9.2	5.0	10.2	5.7	0.39	8.8	4.4	12.2	6.6	9	0.09	9.5	5.4	8.6	4.3	3	0.46
Total body fat, %	26.0	9.0	26.2	9.8	0.94	26.4	9.3	30.5	9.2	9	0.16	25.8	8.9	22.6	8.9	3	0.20
Fat mass index, kg/m^2	4.2	2.1	4.4	2.4	0.70	4.1	2.0	5.3	2.8	9	0.13	4.3	2.2	3.6	1.7	3	0.23
Fat mass ratio	1.11	0.20	1.25	0.21	0.001	1.10	0.19	1.21	0.25	10	0.07	1.13	0.20	1.28	0.16	4	0.004
Lean body mass, kg	24.6	4.4	26.9	4.8	0.003	23.3	3.3	25.7	4.2	9	0.052	25.6	5.0	27.9	5.2	3	0.014
LBMI, kg/m^2	11.3	1.1	11.6	1.2	0.20	10.9	0.9	11.3	1.0	9	0.16	11.7	1.1	11.8	1.2	3	0.51
ALM, kg	12.0	2.3	13.4	2.5	0.001	11.4	1.7	12.8	2.2	12	0.052	12.4	2.7	13.9	2.6	6	0.004
ALMI, kg/m^2	5.5	0.6	5.8	0.6	0.02	5.3	0.5	5.6	0.6	12	0.07	5.6	0.6	5.9	0.7	6	0.08
BMC, g	1095	259	1259	299	0.001	1064	235	1239	332	9	0.06	1116	277	1274	274	3	0.002
BMD, g/cm^2	0.809	0.068	0.863	0.077	<0.001	0.810	0.060	0.862	0.089	9	0.03	0.808	0.074	0.864	0.067	3	<0.001
BMD, z-score	−0.06	0.65	0.43	0.80	0.001	−0.25	0.54	0.19	0.83	9	0.07	0.07	0.70	0.63	0.73	3	0.002
BMDth left, g/cm^2	0.838	0.086	0.904	0.108	0.001	0.802	0.069	0.858	0.114	9	0.06	0.865	0.089	0.941	0.090	3	0.003
BMDth left, z-score	−0.06	0.73	0.44	1.03	0.004	−0.51	0.46	−0.10	0.97	9	0.11	0.26	0.73	0.88	0.86	3	0.013
BMDth right, g/cm^2	0.833	0.082	0.902	0.105	<0.001	0.801	0.072	0.861	0.105	9	0.04	0.857	0.081	0.936	0.094	3	0.002
BMDth right, z-score	−0.11	0.71	0.39	1.00	0.004	−0.52	0.52	−0.12	0.92	9	0.10	0.20	0.68	0.80	0.88	3	0.012

Continued

Table 3 Continued

Variables, units	All					Female					Male				
	EP/ELBW (n=54) and TB (n=54)					EP/ELBW (n=26) and TB (n=25)					EP/ELBW (n=28) and TB (n=29)				
	Mean	SD	Mean	SD	P value*	Mean	SD	Mean	SD	m	P value†	Mean	SD	Mean	SD	m	P value‡
BMD spine, g/cm^2	0.822	0.101	0.836	0.100	0.45	0.852	0.101	0.859	0.124	9	0.85	0.799	0.097	0.817	0.073	3	0.39
BMD spine, z-score	−0.06	0.69	−0.13	0.88	0.70	−0.24	0.71	−0.35	1.04	9	0.69	−0.07	0.66	0.06	0.68	3	0.99

*Mixed linear model (MLM).
†MLM comparing female EP/ELBW and TB.
‡MLM comparing male EP/ELBW and TB.
ALM, appendicular lean mass; ALMI, appendicular lean mass index; BMC, bone mineral content; BMD, bone mineral density; BMDth, total hip bone mineral density; BMI, body mass index; EP/ELBW, extremely preterm born/extremely low birth weight; LBMI, lean body mass index; STR, subscapular- triceps skinfold ratio; TB, term born; WHtR, waist-to-height ratio; m, missing; Fat mass ratio, (arms+legs fat mass)/truncal fat mass.

to significantly lower ALMI (p=0.02), but LBMI did not differ between the groups.

When adjusting for PA, the mean differences in ALM, BMC and BMD were reduced by 20% and the mean differences in BMD z-score by 36%. The measures for truncal fat deposit (STR and FM ratio) remained similar or were only slightly reduced (table 4).

Small for gestational age

Twenty of the EP/ELBW children (13 men and 7 women) were born SGA. Their mean (95% CI) height z-score was 0.88 (0.33 to 1.43) units lower than those who were not SGA. LBM, ALM, BMC, BMD and regional BMD were close to significantly reduced in the SGA group but not when comparing the respective values normalised for height^2 or z-scores (online supplementary file).

Blood samples and puberty

We found no statistically significant group differences in unadjusted or seasonally adjusted D vitamin values. The values for testosterone, LH and FSH did not differ significantly between the EP/ELBW and TB boys, and the values of oestradiol, LH and FSH did not differ significantly between the respective groups of girls. There were no significant differences in reported puberty between the EP/ELBW and TB stratified by gender (online supplementary file).

PA and body composition

Increased PA was associated with statistically significantly lower fat components (%BF and FMI) and higher BMDth z-scores in the total group of participants (table 5).

Analyses of interaction were performed to investigate if associations between PA and body composition differed in the EP/ELBW compared with the TB control group. We found there was an overall tendency for PA to have less positive effect on ALM, ALMI, total BMD z-score and BMDth z-scores in the EP/ELBW-born children compared with the TB children (table 5); however, this was statistically significant only for the BMDth z-scores.

DISCUSSION

Our main findings were that the EP/ELBW-born children were less physically active and that the EP/ELBW-born children had an unfavourable body composition with increased truncal fat deposit, less skeletal muscle mass and lower BMD compared with the TB controls. The association between PA and body composition was weaker in the EP/ELBW than the TB group.

Exercise and participation in sports activities

Our results are in line with other studies that report less PA among ELBW-born or very low BW-born children[24] or young adults.[25 26] However, Welsh *et al*[18] did not reveal differences between school-children born before 25 weeks GA and TB controls when PA was measured by accelerometers.[18] Differences in methodology as well as population lifestyle factors could explain these diverging

Table 4 Results from mixed linear regression analyses of bone mineral density, skeletal muscle mass, fat component and fat distribution measures in 47 EP/ELBW-born children and their 49 term-born age-matched and gender-matched controls in the Western Norway health region in 1999–2000 that were examined in 2010–2011

	EP/ELBW (n=47)		TB (n=49)				
Variables, units	Mean	95% CI	Mean	95% CI	Model*	Difference†	P value
BMC, g	1096	(1016 to 1176)	1256	(1177 to 1334)	1	−160	0.001
					2	−88	0.001
					3	−70	0.006
BMD, g/cm^2	0.809	(0.788 to 0.830)	0.863	(0.843 to 0.884)	1	−0.054	<0.001
					2	−0.039	<0.001
					3	−0.032	0.001
BMD, z-value	−0.07	(−0.28 to 0.14)	0.43	(0.22 to 0.64)	1	−0.50	0.001
					2	−0.33	0.001
					3	−0.21	0.04
BMDth left, z-score	−0.07	(−0.34 to 0.09)	0.44	(0.18 to 0.69)	1	−0.52	0.004
					2	−0.38	0.011
					3	−0.20	0.19
BMDth right, z-score	−0.12	(−0.37 to 0.13)	0.38	(0.14 to 0.63)	1	−0.51	0.004
					2	−0.39	0.012
					3	−0.20	0.19
BMD spine, z-score	−0.06	(−0.29 to 0.17)	−0.13	(−0.35 to 0.10)	1	0.06	0.70
					2	0.22	0.10
					3	0.28	0.054
ALM, kg	12.0	(11.2 to 12.7)	13.4	(12.7 to 14.1)	1	−1.4	0.001
					2	−0.9	0.004
					3	−0.7	0.03
ALMI, kg/m^2	5.5	(5.3 to 5.7)	5.8	(5.5 to 5.9)	1	−0.3	0.02
					2	−0.2	0.03
					3	−0.2	0.19
Body fat, %	26.0	(23.3 to 28.7)	26.2	(23.5 to 28.8)	1	−0.2	0.94
					2	0.0	0.97
					3	−1.1	0.38
Fat mass ratio	1.11	(1.05 to 1.17)	1.25	(1.19 to 1.30)	1	−0.13	<0.001
					2	−0.14	0.001
					3	−0.13	0.001
STR	0.78	(0.72 to 0.85)	0.69	(0.63 to 0.76)	1	0.09	0.04
					2	0.09	0.04
					3	0.09	0.049

*Comparing the EP/ELBW and TB pairs: model 1: unadjusted; model 2: adjusted for height z-score, weight z-score and parental-reported puberty; model 3: adjusted for height z-score, weight z-score, parental-reported puberty and physical activity.
†Estimate of difference between EP/ELBW-born and term-born children.
ALM, appendicular lean mass;ALMI, appendicular lean mass index; BMC, bone mineral content; BMD, bone mineral density; BMDth, total hip bone mineral density; EP/ELBW, extremely preterm/extremely low birth weight; STR, subscapular-triceps skinfold ratio; TB, term born; Fat mass ratio, (arms+legs fat mass)/truncal fat mass.

results in that potential differences in PA may become more apparent in societies where children in general are more active.

Several factors have been suggested to contribute to lower PA in preterm-born children, including reduced muscle mass, altered muscle fibre composition, reduced lung function and reduced physical fitness.[27] Other important aspects are their increased risk of shortcomings due to clumsiness, hyperactivity, inattention and lower physical confidence.[28] Our findings imply that EP/ELBW-born children are less inclined to attend team sports but instead prefer to perform PA alone or together

Table 5 Results from mixed linear regression analyses of effect of leisure time physical activity on body composition in 47 extremely preterm (EP) born children and their 49 age-matched and gender-matched term-born (TB) controls born in year 1999–2000 in the Western Norway health region and examined in 2010–2011 as part of the Project Extreme Prematurity

Variables, units	EP born		TB					Physical activity			Physical activity EP compared with TB		
	Mean	95% CI	Mean	95% CI	Difference*	95% CI	P value	Effect †	95% CI	P value	Effect‡	95% CI	P value
Weight, z-score	−0.34	(-0.63, to 0.05)	−0.13	(−0.43 to 0.16)	−0.20	(−0.60 to 0.20)	0.32	−0.09	(−0.28 to 0.11)	0.39	−0.03	(−0.44 to 0.36)	0.88
BMI, z-score	−0.19	(−0.47 to 0.09)	−0.21	(−0.49 to 0.07)	−0.02	(−0.39 to 0.43)	0.92	−0.10	(−0.29 to 0.09)	0.28	0.03	(−0.36 to 0.42)	0.89
FMI, kg/m^2	4.2	(3.5 to 4.9)	4.4	(3.7 to 5.0)	−0.2	(−1.1 to 0.8)	0.70	−0.9	(-1.3, to 0.4)	<0.001	0.5	(−0.5 to 1.4)	0.32
Total body fat, %	26.0	(23.3 to 28.7)	26.1	(23.5 to 28.8)	−0.16	(−4.0 to 3.7)	0.94	−4.1	(-6.0, to 2.1)	<0.001	2.3	(−1.6 to 6,2)	0.25
ALMI, kg/m^2	5.5	(5.3 to 5.7)	5.8	(5.6 to 5.9)	−0.3	(-0.5, to 0.1)	0.02	0.1	(−0.1 to 0.2)	0.44	−0.3	(-0.6, to 0.1)	0.012
LBMI, kg/m^2	11.3	(11.0 to 11.6)	11.6	(11.3 to 11.8)	−0.3	(−0.7 to 0.2)	0.20	0.1	(−0.1 to 0.4)	0.27	−0.6	(-1.1, to 0.1)	0.02
STR	0.78	(0.72 to 0.85)	0.69	(0.63 to 0.76)	0.09	(0.00 to 0.17)	0.04	0.005	(−0.04 to 0.05)	0.83	−0.09	(−0.18 to 0.01)	0.07
WHtR	0.44	(0.43 to 0.45)	0.44	(0.43 to 0.45)	0.00	(−0.01 to 0.03)	0.79	−0.01	(−0.02 to 0.00)	0.11	−0.00	(−0.02 to 0.02)	0.71
Fat mass ratio	1.11	(1.05 to 1.17)	1.25	(1.19 to 1.30)	−0.13	(-0.21, to 0.06)	0.001	0.00	(−0.04 to 0.05)	0.84	0.04	(−0.05 to 0.13)	0.42
BMC, g	1096	(1016 to 1176)	1256	(1177 to 1335)	−160	(-252, to 67)	0.001	14	(−41 to 69)	0.63	−126	(-245, to 6)	0.04
BMD, g/cm^2	0.809	(0.788 to 0.830)	0.863	(0.843 to 0.884)	−0.054	(-0.078, to 0.030)	<0.001	0.008	(−0.007 to 0.022)	0.28	−0.034	(-0.065, to 0.003)	0.03
BMD, z-score	−0.07	(−0.28 to 0.14)	0.43	(0.22 to 0.64)	−0.50	(-0.78, to 0.22)	<0.001	0.09	(−0.07 to 0.25)	0.27	−0.39	(-0.71, to 0.07)	0.02
BMD, spine z-score	−0.06	(−0.29 to 0.17)	−0.13	(-0.35, to 0.10)	0.06	(−0.26 to 0.39)	0.70	0.03	(−0.15 to 0.21)	0.73	−0.23	(−0.59 to 0.13)	0.20
BMDth left, z-score	−0.07	(−0.33 to 0.19)	0.44	(0.18 to 0.69)	−0.51	(-0.84, to 0.17)	0.004	0.21	(0.02 to 0.40)	0.03	−0.53	(-0.91 to 0.15)	0.007
BMDth right, z-score	−0.12	(−0.37, 0.14)	0.38	(0.14, 0.63)	−0.50	(-0.83, -0.17)	0.004	0.24	(0.05, 0.42)	0.001	−0.50	(-0.87 to -0.13)	0.009

*Unadjusted difference between EP born and TB.
†Estimated overall effect of physical activity.
‡Estimated difference in effect of PA on EP born compared with TB (interaction term). Boldface denotes significant group differences.
ALMI, appendicular lean mass index; BMC, bone mineral content; BMD, bone mineral density; BMDth, total hip bone mineral density; LBMI, lean body mass index; PA, physical activity; STR, subscapular-triceps skinfold ratio; WHtR, waist-to-height ratio; Fat mass ratio, (arms+legs fat mass)/truncal fat mass.

with family members. This could reflect the neuromuscular and social interaction difficulties these children may experience.

Habits of PA track from childhood into adulthood,[29] and therefore, our results suggest that the long-term health of EP/ELBW-born children may be negatively affected.

Body composition

Preterm-born children have been reported to have increased truncal fat deposit and insulin resistance, established risk factors for developing type 2 diabetes mellitus.[30 31] Our study supports these observations since the EP/ELBW-born children had a lower FM ratio and a close to significantly higher STR, indicating greater truncal fat deposits.

There is a positive association between BW and muscle strength, which is maintained during life.[32] Skeletal muscle mass, fat-free mass and muscle strength have been found to be reduced in children and adults born preterm compared with those born at term.[26 27 33] This is in line with our results, where the EP/ELBW-born children had approximately 1 kg less skeletal muscle mass than the TB children.

In addition to providing strength and mobility, skeletal muscle is insulin sensitive and an important regulator of glucose metabolism and therefore relevant in preventing cardiovascular and metabolic disease.[34] We suggest that the EP/ELBW-born children's lower muscle mass may negatively affect long-term health outcome by reducing their engagement and abilities in PA and by contributing to an ineffective metabolism.

There is an association between low BW and low peak bone mass later in life.[11 35 36] In our study, the mean total BMD z-score and BMDth z-scores in the EP/ELBW-group were within normal ranges but nevertheless lower than in the TB group. As reduced peak BMD is regarded the most important determinant of osteoporosis and fractures in later adulthood,[37] the EP/ELBW-born children may be at increased risk.

Mean BMD z-score in the TB group was greater than expected, especially among the men. The reason may be that the TB controls were more active than the children in the reference material[38] or that there are secular trends towards greater BMD values in Norwegian boys.

Measures of body composition are influenced by the size of the body. BMD is correlated with weight, height and puberty, and these measures were adjusted for by height and weight z-score in addition to parental reported puberty. However, DXA-derived BMD is based on the two-dimensional projected area of a three-dimensional structure, and it is possible that smaller bones was found to have lower BMD than larger bones. The skeletal muscle mass (ALM and LBM)) and FM were normalised for height squared, and we additionally adjusted ALMI for height and weight z-score to take into account the height and weight difference between the individuals at the given age (table 4, model 2). FM ratio and STR are less influenced by height and weight as reflected in table 4.

PA and body composition

PA is associated with numerous health benefits on a range of non-communicable diseases.[13 14] However, EP/ELBW-born children's benefits from exercise are not well studied.

The associations between PA and bone mineral and skeletal muscle mass accrual were weaker in the EP/ELBW than in the TB group. The less enduring and less vigorous physical engagement in PA among the EP/ELBW-born children may be one explanation, but it may also imply that EP/ELBW-born children benefit less from exercise compared with TB.

Nevertheless, the EP/ELBW-born children should be encouraged to be more physically active to achieve their potential peak bone and muscle mass.

The impact of the perinatal stress the preterm born individuals are exposed to is far from fully understood. One may hypothesise that early epigenetic adaptation and metabolic programming can explain later development of an unfavourable body composition.[39] Future studies should try to establish optimal growth patterns for preterm children to facilitate better and individualised nutritional treatment. Furthermore, studies are needed to assess to what extent the frequency, volume and intensity of PA might improve body composition of the preterm born children.

Strengths and limitations

The major strength of this study was the population-based and controlled design with a relatively high rate of attendance and that the participants were representative of the complete cohort. Recruitment of TB controls was based on the 'next-born subject principle', minimising the risk of selection bias. Potential bias introduced by a two-centre design was limited by paired statistical analysis with EP/ELBW and TB controls who were recruited and examined at the same institution. Moreover, potential inaccuracies introduced by collecting data on exercise habits and pubertal staging by suboptimal methods are likely to pertain similarly to the EP/ELBW and TB groups, thus allowing for group comparisons.

The EP/ELBW children were recruited based on either GA below <28 weeks or BW less than 1000 g irrespectively of GA. Therefore, the results cannot be generalised to EP-born individuals in general.

The exercise habits were determined by questionnaires rather than more objective methods like accelerometers and diaries, which represent a limitation to the study. Especially, we assume the report on unstructured exercise activity to be inaccurate. The association between PA and body composition must therefore be interpreted with caution.

Pubertal stage was not assessed by clinical examination, but rather with parental report, and the dietary intake for calcium and vitamin D was not recorded, factors that can

influence the interpretation of BMD. However, a recent meta-analysis concluded that preterm born children enter puberty at the same age as term born children.[40] In addition, our paired analysis on the question regarding puberty did not find differences between the groups.

The p value has not been formally adjusted for multiple comparison and subsequent studies should be performed to confirm our observed associations.

CONCLUSIONS

Compared with TB controls, the EP/ELBW-born school children were less physically active, and our study suggests that they had an unfavourable body composition with increased truncal fat, less skeletal muscle mass and reduced BMD. Physical activity was less associated with mineral and skeletal muscle mass accrual in the EP/ELBW-born group.

What is known about the subject?

- Physical activity is associated with several health benefits and has preventive effects on several non-communicable diseases like osteoporosis and cardiometabolic disease.
- There is a positive association between birth weight and muscle strength and peak bone mass, which is maintained across the life course.
- We lack knowledge on how physical activity impacts body components in children born extremely preterm or at extremely low birth weight.

What this study adds?

- The children born extremely preterm or with extremely low birth weight (EP/ELBW) were less physically active than term born children.
- The children born EP/ELBW had an unfavourable body composition with less muscle mass, reduced bone mineral density and increased truncal fat.
- Physical activity was less associated with mineral and skeletal muscle mass accrual in the EP/ELBW-born group compared with term-born controls.

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Methods:

Anthropometry

Height was recorded without shoes to the nearest 0.1 cm using a fixed stadiometer. Weight was measured with minimal clothing on, without shoes, to the nearest 0.1 kg using digital scales. Subscapular and triceps skinfolds were measured using a Holtain Skinfold Caliper. Waist circumference was measured with a tape on bare skin with the participant in a standing position.

Blood samples

Blood for serum bone markers 25-hydroxy vitamin D, (25(OH)D)), 1,25 dihydroxy-vitamin D (1,25(OH)D), insulin-like growth factor 1 (IGF-1), insulin-like growth factor-binding protein 3 (IGFBP-3) and parathyroid hormone (PTH) were drawn at the consultation, centrifugated within 1 hour and separated before the serum were stored in a frozen biobank holding -80 ^{o}C. In 2015, the serum was later analyzed in one run at the hormone laboratory at Haukeland University hospital. 25(OH)D was analyzed by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS, In-house method.) (32). 1,25(OH)2vitD was determined by radioimmunoassay from Immunodiagnostic Systems. IGF-1 level, IGFBP-3 and PTH levels were determined using chemiluminescence immunometric assay from Siemens IMMULITE 2000.

In 2018, stored serum was analyzed in one run to obtain values for testosterone, estradiol, luteinizing hormone (LH) and follicle-stimulating hormone (FHS). Estradiol and testosterone were analyzed by LC-MS/MS (In-house method) and LH and FSH by chemiluminescence immunometric assay, Siemens IMMULITE 2000.

Supplementary table 1 Anthropometry and body composition parameters results according to weight percentile at birth for the 54 extremely preterm or extremely low birthweight children born in the Western Norway Health Region in 1999 – 2000 that were examined in 2010-11

Variables, (*units*), *statistic*	**SGA**	**m**	**Not SGA**	***m***	***p*** [a)]
Total subjects, *n*	20		34		
Male gender, *n*	13	0	15	0	.14
Gestational age (weeks), *median, (range)*	28 (24-27)	0	26 (24-31)	0	< .001
Birthweight (g), *mean (SD)*	724 (143)	0	910 (155)	0	< .001
Anthropometry					
Height (cm), *mean (SD)*	142.6 (6.0)	0	149.2 (8.0)	0	.002
Height, z-score, *mean (SD)*	-0.96 (0.98)	0	-0.09 (0.97)	0	.002
Weight (kg), *mean (SD)*	36.2 (8.9)	0	39.8 (7.8)	0	.12
Weight, z-score, *mean (SD)*	-0.66 (1.18)	0	-0.15 (0.99)	0	.17
BMI (kg/m^2), *mean (SD)*	17.6 (3.1)	0	17.7 (2.3)	0	.90
BMI, z-score, *mean (SD)*	-0.24 (1.15)	0	-0.16 (1.01)	0	.78
Waist circumference (mm), *mean (SD)*	65.1 (8.9)	0	65.5 (7.7)	3	.87
Subscapular fold (mm), *mean (SD)*	9.1 (4.4)	0	8.4 (3.7)	4	.59
Triceps skinfold (mm), *mean (SD)*	11.1 (4.1)	1	11.4 (4.2)	4	.79
STR, *mean (SD)*	0.82 (0.30)	1	0.76 (0.19)	4	.33
WHtR, *mean (SD)*	0.46 (0.05)	0	0.44 (0.04)	3	.16
DXA					
Fat mass (kg), *mean (SD)*	8.6 (5.4)	3	9.6 (4.7)	4	.49
Total body fat (%), *mean (SD)*	25.7 (8.0)	3	26.1 (9.6)	4	.88
FMI (kg/m^2), *mean (SD)*	4.1 (2.3)	3	4.3 (2.0)	4	.82
Fat mass ratio, *mean (SD)*	1.12 (0.25)	4	1.11 (0.17)	5	.93
Lean body mass (kg), *mean (SD)*	22.9 (3.7)	3	25.6 (4.6)	4	.045
LBMI (kg/m^2), *mean (SD)*	11.2 (1.1)	3	11.4 (1.1)	4	.51
ALM (kg), *mean (SD)*	11.0 (1.6)	5	12.6 (2.5)	7	.03
ALMI (kg/m^2), *mean (SD)*	5.3 (0.4)	5	5.6 (0.6)	7	.19
BMC (g), *mean (SD)*	966 (230)	3	1168 (248)	4	.009
BMD (g/cm^2), *mean (SD)*	0.779 (0.063)	3	0.826 (0.065)	4	.02
BMD, z-score	-0.29 (0.69)	3	0.06 (0.60)	4	.07
BMDth left (g/cm^2), *mean (SD)*	0.800 (0.075)	3	0.859 (0.086)	4	.02
BMDth left, z-score, *mean (SD)*	-0.29 (0.67)	3	0.06 (0.75)	4	.12
BMDth right (g/cm^2), *mean (SD)*	0.798 (0.067)	3	0.853 (0.083)	4	.02
BMDth right, z-score, *mean (SD)*	-0.32 (0.59)	3	0.01 (0.74)	4	.12
BMD spine (g/cm^2), *mean (SD)*	0.762 (0.075)	3	0.856 (0.010)	4	.002
BMD spine, z-score, *mean (SD)*	-0.38 (0.60)	3	0.12 (0.69)	4	.02

Abbreviations: ALM: appendicular lean mass; ALMI: appendicular lean mass index; BMC: bone mineral content; BMD: bone mineral density; BMDth: total hip BMD; DXA: Dual-energy X-ray absorptiometry; FMI: fat mass index; Fat mass ratio: (arms + legs fat mass)/truncal fat mass; LBMI: lean body mass index; m: missing; SGA: small for gestational age; SD: standard deviation; STR: subscapular- triceps skinfold ratio; WHtR: waist to height ratio.

a) Independent sample t-test or Mann-Whitney U test as appropriate.

Supplementary table 2 Comparing sex hormone and d-vitamin level between the extremely preterm/extremely low birthweight born children and their age- and gender matched term-born controls (TB) born year 1999 – 2000 in the Western Norway Health Region and examined in 2010-11

	All					Female						Male					
	EP/ELBW n = 50		TB n = 48			EP/ELBW n = 25		TB n = 22				EP/ELBW n = 25		TB n = 26			
Hormone, *unit*	**Mean**	**SD**	**Mean**	**SD**	***p*[a)]**	**Mean**	**SD**	**Mean**	**SD**	**m**	***p*[b)]**	**Mean**	**SD**	**Mean**	**SD**	**m**	***P*[c)]**
D-vit, *nmol/L*	52.1	17.2	54.0	16.4	.43	54.0	16.0	52.0	16.2	2	.78	50.2	18.5	55.6	16.7	2	.21
Testosterone, *nmol/L*	1.8	3.5	1.3	2.3	.56	-	-	-	-	-	-	1.8	3.5	1.3	2.3	3	.56
Estradiol, *pmol/L*	88.3	96.2	74.6	80.3	.79	88.3	96.2	74.6	80.3	18	.79	-	-	-	-	-	-
LH, *IE/L*	1.2	1.3	1.2	1.2	.95	1.9	1.6	1.8	1.6	17	.96	0.78	0.70	0.84	0.62	8	.72
FSH, *IE/L*	2.4	1.5	2.6	1.6	.56	3.2	1.6	3.8	1.	13	.29	1.8	1.2	1.8	1.1	4	.98

Abbreviations D-vit: 25(OH)D vitamin; EP/ELBW: extremely preterm/extremely low birthweight; LH: luteinizing hormone FSH: follicle-stimulating hormone; m: missing; SD; standard deviation.

a) p-value for differences between the EP/ELBW and TB by mixed linear model

b) p- value for differences between the female EP/ELBW and TB by mixed linear model

c) p- value for differences between the female EP/ELBW and TB by mixed linear model

Paper II

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Predicting physical activity in a national cohort of children born extremely preterm

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ABSTRACT

Predicting physical activity in a national cohort of children born extremely preterm.

Objectives: To compare physical activity among school-aged children born extremely preterm or with extremely low birthweight (EP/ELBW) to term-born children, and to identify early predictors for physical inactivity in the EP/ELBW-children.

Methods: A national cohort born during 1999–2000 at gestational age < 28 weeks or birthweight <1000 g and term-born controls were assessed. EP/ELBW-children without neurodevelopmental disabilities were labeled "healthy". At five years, we examined the EP/ELBW-children's motor, mental and intellectual functioning using the *Movement Assessment Battery for Children* (MABC), *The Strength and Difficulties Questionnaire* (SDQ) and *The Wechsler Preschool and Primary Scale of Intelligence-revised*. At 11 years, the parents reported their children's physical activity (PA) in questionnaires.

Results: Information was obtained from 231/372 EP/ELBW and 57/61 term-born children. At 11 years, EP/ELBW-children had fewer exercise events per week, were less engaged in team sports, had lower endurance, lower sports proficiency, and were less vigorous during PA than term-born children ($p < 0.05$). Low sports proficiency in the healthy EP/ELBW-children at 11 years was predicted (odds ratio; 95% confidence interval) by abnormal MABC-score (3.0; 1.0 to 8.7), and abnormal SDQ-score (4.0; 1.6 to 10.0) at 5 years. Lower endurance at PA was predicted by abnormal MABC-score (2.6; 1.0 to 6.6), abnormal SDQ-score (3.0; 1.4 to 6.5), and borderline intellectual functioning (4.2; 1.8 to 10.1).

Conclusions: Eleven-year-old EP/ELBW-children were less physically active than term-born. In healthy EP/ELBW-children, impaired motor coordination, borderline intellectual functioning and behavioral problems at 5 years of age predicted unfavorable PA habits at 11 years.

1. Introduction

Over the past decades, advances in neonatal medicine have improved survival rates of extremely preterm (EP) (<28 weeks of gestation) and extremely low birthweight (ELBW) (<1000 g) infants [1]. These children are at risk of major sequelae, such as cerebral palsy (CP), severe cognitive impairment, blindness and deafness [2]. Such disabilities are often recognized at an early age, with supportive services usually established before school age. However, children born at this early stage are also challenged by more subtle problems, such as motor

Abbreviations: CI, confidence interval; DCD, developmental coordination disorder; EP/ELBW, extremely preterm/extremely low birthweight; FIQ, full-scale intelligence quotient; FIQ70–84, full-scale intelligence quotient of 70–84; MABC, *Movement Assessment Battery for Children*; MABC5, *Movement Assessment Battery for Children*-score under the 5th percentile; NDD, neurodevelopmental disability; PA, physical activity; SD, standard deviation; SDQ, *Strength and Difficulties Questionnaire*; TDS, Total Difficulties Score; TDS90, TDS ≥ the 90th percentile of reference children; WPPSI-R, *Wechsler Preschool and Primary Scale of Intelligence-revised*

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coordination problems [3,4], minor cognitive impairment, inattention, hyperactivity and difficulties in social interactions [5]. Such disabilities can pass unnoticed, and influence school performances [6] as well as skills and motivation needed to participate in leisure time physical activity (PA), play and sports [7].

Population studies have shown that PA is associated with numerous health benefits and that PA prevents development of diseases like cardiometabolic and psychiatric disorders [8], conditions increasingly recognized as overrepresented in preterm-born adults [9]. Some studies find children born preterm to be less physically active than term born children, [10,11] while other studies find them to be similarly active [12,13]. Moreover, habits of PA tend to track from childhood to adulthood [14]. If habits are to be altered, early interventions are clearly preferable [15]. We therefore need more information on the PA habits of EP/ELBW-born children and we should search for early predictors of later childhood inactivity.

In this study, we aimed to compare PA in a national cohort of 11-year-old EP/ELBW schoolchildren with those of term-born children. Moreover, we investigated if structured data on motor, cognitive and mental function obtained at 5 years of age could predict habits of PA at 11 years of age in the EP/ELBW children who were considered to be healthy.

2. Methods

2.1. Participants and study design

This was a national prospective observational study of all infants born in Norway during 1999–2000, with gestational age (GA) < 28 weeks and/or birthweight (BW) < 1000 g. The inclusion of the preterm born children, data collection and outcome at discharge from the neonatal intensive care unit and at two, five and 11 years of age, have been described in previous communications [2,16–18].

At five years of age the EP/ELBW children's motor- and intellectual functioning were assessed, and their parents completed questionnaires regarding sociodemographic measures, mental health and behavioral characteristics, general health issues, and use of medication.

At 11 years of age, term-born children were recruited as controls for a regional subsample of the EP/ELBW children who had been born within the Western Norway Regional Health Authority. The term-born children were identified from birth protocols at the maternity ward [18] and were invited as the next-born child of the same gender as the EP/ELBW child, with GA > 37 weeks and BW > 3000 g, corresponding to the Norwegian 10-centile [19]. Information on PA was provided by standardized questionnaires filled in by the parents at 11 years of age (Fig. 1).

Skromme et al. previously described early characteristics of the EP/ELBW children who participated vs. those who did not participate at 11 years of age [18]. The children who did not participate (140/372) were overall more vulnerable, with a higher rate of CP, blindness or deafness at five years of age.

2.2. At five years of age; questionnaires, tests and classifications

2.2.1. The Movement Assessment Battery for Children (MABC)

Physiotherapists assessed the EP/ELBW children's motor function using the MABC test. [20] Total age-specific motor impairment scores range from 0 to 40, increasing with poorer function. The MABC manual defines age specific abnormal total scores, presented as scores below the 5th percentile (MABC5), indicating motor coordination problems [21]. Validity and reliability of the MABC is high [22]. The test is commonly used to identify children with developmental coordination disorder (DCD), defined as a marked impairment in the development of motor coordination that is not explained by mental retardation and that is not due to a known physical disorder [23].

2.2.2. Gross motor function classification system (GMFCS)

Pediatricians classified the EP/ELBW children with CP according to the GMFCS. This is a 5-level classification system describing the gross motor function of children and youth with CP based on their self-initiated movements. Level 1 indicates walking abilities without restrictions whereas level 5 indicate very limited mobility abilities even with the use of assistive technology [24].

2.2.3. Wechsler Preschool and Primary Scale of Intelligence-revised (WPPSI-R)

Psychologists examined the EP/ELBW children's intellectual function with the WPPSI-R. The test provides a full-scale intelligence quotient score (FIQ) with a mean values of 100 and standard deviation (SD) of 15 point, that represents the child's general intellectual ability [25]. The correlation between the WPPSI-R and other comparable tests is strong, and the WPPSI-R has a high inter-rater agreement and test-retest stability [25,26]. In this study a borderline IQ is defined as a FIQ between 70 and 84 points (FIQ70–84).

3. The Strength and Difficulties Questionnaire (SDQ)

Parent-reported SDQ is a behavioral screening questionnaire for 4–17-year-old children with good psychometric properties [27]. The SDQ is frequently used when investigating mental health in EP/ELBW children [5,28,29]. The questionnaire consists of 20 items distributed into four subscales; emotional problems, hyperactivity/inattention, conduct problems, and peer problems. The four subscales compute a Total Difficulties Score (TDS) ranging from 0 to 40. TDS ≥ the 90th percentile (TDS90) of the reference children was considered as a risk of having a mental health problem as recommended by Goodman [30,31].

3.1.1. Neurodevelopmental disability (NDD)

Visual function and hearing were determined from the clinical examination or previous examination at the public health care clinics.

For the purpose of this study neurodevelopmental disability (NDD) were defined as one or more of the following: CP classes 1 to 5 on the GMFCS, FIQ more than 2 standard deviations (SD) below the reference mean value of 100 (<70 on the WPPSI-R), severe visual impairment or legal blindness, or complete deafness or need of hearing aid.

A healthy-EP/ELBW child was defined as an EP/ELBW child with no NDD or minor sensory disability at five years of age (i.e. no CP, FIQ ≥ 70, strabismus or refractive error, or mild hearing loss). Further details regarding data collection on NDD are provided in Appendix A.

3.2. At 11 years of age; the questionnaires mapping physical activity

We collected information on participation in sports clubs, team sports or other physical activities. The parents graded the children's proficiency or clumsiness and how vigorous and enduring the child was, compared to their peers in sports and play. In addition, a validated question from *the World Health Organization health behavior in schoolchildren survey* served to determine the frequency of leisure time physical activity: *Apart from at school, how often do you usually exercise so much that you get out of breath or sweat?* [32].

3.3. Ethics

The Regional Committee on Medical Research Ethics granted ethical approval of the protocol, and the mothers gave written, informed consent.

3.4. Statistics

Summary statistics are presented as means and standard deviations

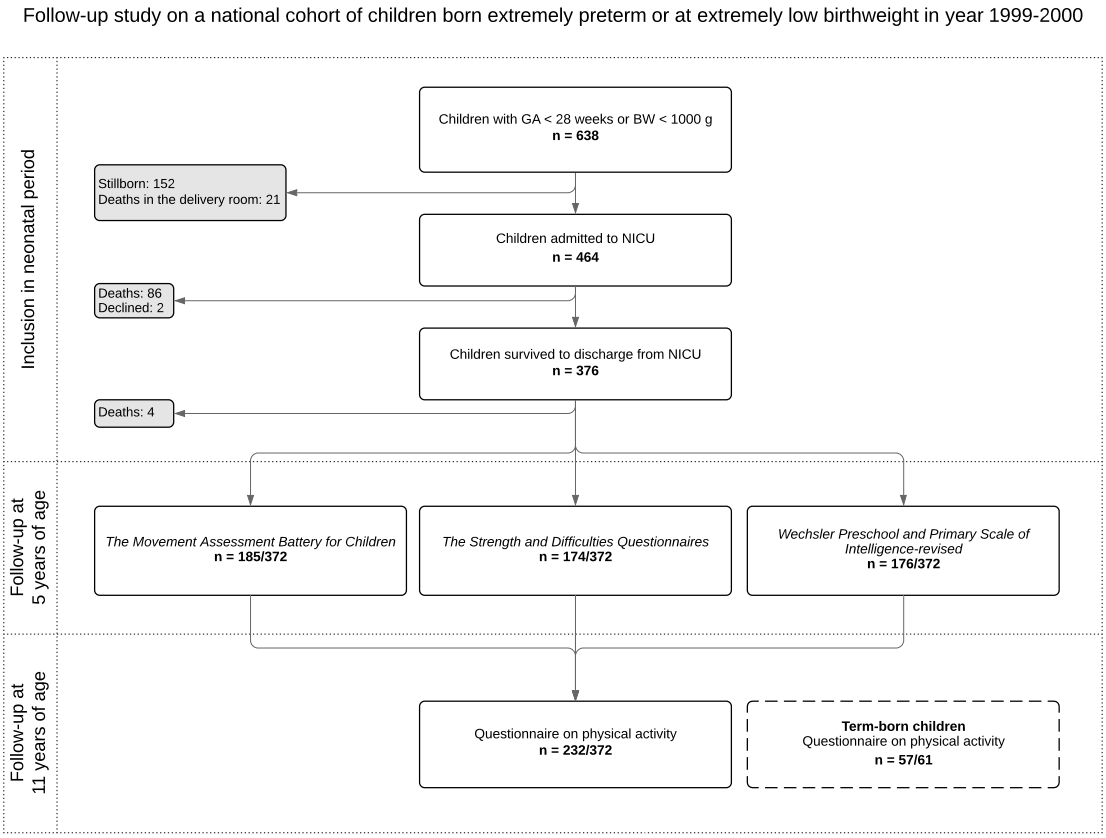

Fig. 1. The recruitment of subjects participating in a follow-up study of a national cohort of children born extremely preterm or at extremely low birthweight in year 1999–2000.
Abbreviations: BW: birthweight; GA: gestational age; NICU: neonatal intensive care unit.

(SD) or medians with interquartile ranges. Group comparisons were performed with the χ^2-exact test and the Mann-Whitney *U* test. Results on PA were adjusted for socioeconomic status (single parenthood and low maternal education level defined as less than years of college education). Small for gestational age (SGA) was defined as under the 10th percentile for gestational age (GA) [19]. Bronchopulmonary dysplasia (BPD) was defined as oxygen dependency at 36 weeks postmenstrual age.

Test results from the MABC-, the SDQ- and the WPPSI-R-test were dichotomized into normal and abnormal test results defined by MABC5, TDS90 and FIQ70–84, respectively.

Multiple logistic regression analyses were used to identify if abnormal motor coordination (MABC5), behavioral problems (TDS90) or borderline intellectual functioning (FIQ70–84) at five years of age could predict outcome regarding PA at 11 years of age for the healthy-EP/ELBW children. The dependent variables on PA used in the analyses were obtained from the questionnaire and dichotomized into "leisure time PA ≤ 1 day/week or >1 day/week", "participating/not participating in organized sports activities", "equal/lower endurance", "more or equal/less vigorous", "average or high/poor proficiency in sports activities", "equal or better/clumsy manual dexterity" and "equal or better/clumsy gross motor function". Prediction of the dependent variables "poor proficiency in sports activities", "clumsy manual dexterity" and "clumsy gross motor function" were adjusted for both borderline intellectual functioning (FIQ70–84) and abnormal motor coordination (MABC5) [33]. Additionally, we adjusted for low maternal education, use of asthma medication at five years of age, BPD and SGA if significant differences were found between the comparing groups (Appendix Table 1). The results are expressed as odds ratios (OR) with 95% confidence intervals (CI).

The study was conducted as part of a long-term follow-up of EP/ELBW children, and statistical power analysis was not conducted with respect to PA, as the number of participants was given by the size of the cohort. $p \leq 0.05$ was considered statistically significant. All analyses were performed using IBM SPSS statistics version 25.

4. Results

4.1. Study population

Data on physical activity at 11 years of age were available for 232 out of 372 eligible EP/ELBW children (115 boys) at mean age (SD) 10.8 (0.4) years and 57 out of 61 eligible term-born (31 boys) controls at the mean (SD) age of 11.7 (0.7) years (Table 1). After excluding the one participant with unknown NDD status (Appendix A), 208/231 children were classified into the healthy-EP/ELBW group and 23/231 children were classified into the disabled-group with NDD.

Table 1
Assessment of 232 surviving extremely preterm/extremely low birthweight (EP/ELBW) children and 57 term-born children participating a nationwide cohort born in Norway during 1999–2000.

Variables	EP/ELBW-born		Term-born		*p*
	n = 232		n = 57		
Male gender, n (%)	115	(49.6)	31	(54.3)	0.516
Birthweight g, mean (IQR)	865	(230)	3687	(685)	<0.001
Bronchopulmonary dysplasia, n (%)	113	(48.7)			
Small for gestational age, n (%)	46	(19.8)			
Patent ductus arteriosus, surgical closure, n (%)	38	(16.4)			
Assessment at 5 years of age					
MABC test assessment, n (%)	185	(79.7)			
MABC score < 5th percentile, n	29				
Full scale IQ assessment (FIQ), n (%)	176	(75.8)			
FIQ < 85 points, n	35				
FIQ < 70 points, n	10				
SDQ assessment, n (%)	174	(75.0)			
TDS ≥ the 90th percentile, n	60				
NDD assessment, n (%)	197	(84.9)			
NDD moderate or severe, n	22				
Asthma medication assessment, n (%)	198	(85.3)			
None, n	156				
Daily use, n	12				
Intermittent use, n	30				
Assessment at 11 years of age					
Mother higher education[a)], n (%)	124	(53.4)	35	(61.4)	0.512
Single parenthood, n (%)	31	(13.3)	2	(3.5)	0.036
Speech therapist (current), n (%)	7	(3.0)	1	(1.8)	1.000
Physiotherapist (current), n (%)	22	(9.4)	1	(1.8)	0.056
Habilitations services (current), n (%)	10	(4.3)	0	(0)	0.219
Reduced mobility at 11 y, n (%)	8	(3.4)	0	(0)	0.363
Current visual impairment, n (%)	53	(22.8)	5	(8.8)	0.016
Blind on eye, n	3		1		
Binoculars, n	54		4		
Current hearing impairment, n (%)	24	(10.3)	2	(3.5)	0.188
Cochlea implant, n	2		1		
Hearing devices, n	8		0		
Hearing and visual impairment, n	6		0		
Asthma at 11 years, n (%)	36	(15.5)	4	(7.0)	0.132
Inhaled corticosteroids, n (%)	21	(9.1)	3	(5.3)	0.433

Abbreviations: IQR: interquartile range; MABC: The Movement Assessment Battery for Children: NDD: neurodevelopmental disability; SDQ: Strength and Difficulties Questionnaires; TDS: total difficulty score; *p*: from χ^2-exact test except independent *t*-test for birthweight.

[a] At least three-year college education or a university degree.

4.2. Physical activity at 11 years of age

Among all EP/ELBW children, 31% exercised ≤1 day/week in their leisure time compared to 14% of term-born children (Table 2). The difference between the groups remained significant after adjusting for socioeconomic status, OR (95% CI) 2.8 (1.2 to 6.5), $p = 0.02$ (Fig. 2).

Healthy-EP/ELBW children were less physically active than term-born (28% vs. 14% exercised ≤1 day/week), were more often reported to have lower physical endurance (36% vs. 2%) and to be less vigorous (22% vs. 7%). Healthy-EP/ELBW children were also more often rated to be clumsier (32% vs. 5%) and to have poorer proficiency (23% vs. 5%) in sports and play, and fewer participated in team sports (48% vs. 72%). The difference in team sport participation was explained by the high rate of participating term-born boys compared to healthy-EP/ELBW boys (80% vs. 50%, $p = 0.003$). All these results remained significant after adjusting for socioeconomic status.

We compared the healthy-EP/ELBW children with those with NDD. In all questions on PA, except questions regarding participation in sports and other activities, more disabled EP/ELBW than healthy-EP/ELBW children reported unfavorable characteristics (Table 2). The results remained significant after adjusting for socioeconomic status.

4.3. Early predictors of physical activity among healthy EP/ELBW children

4.3.1. Motor problems

In the healthy-EP/ELBW group, an abnormal MABC score (MABC5) at five years of age was associated with poorer proficiency at sports, lower endurance, less vigorous PA and clumsiness at 11 years of age. After adjustment for confounders, the result remained significant for poorer proficiency and less vigorous PA (Table 3).

4.3.2. Behavioral problems

An abnormal TDS (TDS90) at five years of age was associated with poorer proficiency at sports, lower endurance, less vigorous PA, and gross motor clumsiness at 11 years of age. A TDS90 was also associated with less participation in organized sports activities outside school. After adjustment for confounders, the result remained significant for poorer proficiency, lower endurance and less vigorous PA (Table 3).

4.3.3. Intellectual function

A borderline intellectual functioning (FIQ70–84) at five years of age was associated with lower endurance, less vigorous PA and poor manual dexterity at 11 years of age. After adjustment for confounders, the result remained significant (Table 3).

5. Discussion

In this national birth cohort, healthy-EP/ELBW schoolchildren were less physically active, had lower endurance and were less vigorous in PA than their term-born peers. They were also more likely to be rated clumsy and to have poorer proficiency at sports. Disabled EP/ELBW children reported even poorer outcome. In healthy EP-born children, impaired motor coordination, borderline intellectual functioning and behavioral problems at 5 years of age predicted unfavorable habits of physical activity at 11 years of age.

5.1. Physical activity

Our results are comparable with other studies that report less PA among unimpaired children born with very low BW or ELBW [10,11,34,35]. However, a study measuring PA by accelerometers did not find differences when comparing schoolchildren born earlier than 25 weeks of gestation and term-born controls [12]. Diverging results may be explained by differences in methodology. Moreover, differences in PA may become more apparent if control groups are recruited from societies where children in general are more physically active [34,36,37].

EP/ELBW children were reported to have lower endurance and to be less vigorous when physically active. Several studies have found EP/ELBW born children and young adults to have a reduced exercise capacity compared to age-matched controls [12,38–41]. Although chronic lung disease and altered breathing patterns during exercise have been described in EP-born populations [12,39,42], impaired lung function and airflow limitation are not considered to be a major contributor to these findings, and several other mechanisms have been highlighted. Head circumference was a significant covariate in a study by Welsh et al., suggesting that reduced exercise capacity may be influenced by neuromuscular impairment [12]. This is supported by Burns et al. who found that motor coordination was the principal determinant of cardiovascular endurance in the ELBW children [40]. Also, a reduced muscle mass in EP-born children may contribute to an earlier onset of metabolic acidosis and lower workload achievements [12]. Given the

Table 2
Comparing questionnaire reported data on physical activity for the extremely preterm/extremely low birthweight born (EP/ELBW) with neurodevelopmental disability (n = 23), the EP/ELBW born without neurodevelopmental disability (n = 208) and term-born controls (n = 57) in the national cohort of Norway in 1999–2000.

Questions on physical activity	EP/ELBW-NDD		EP/ELBW			Term-born		
	N = 23 m = 13, f = 10		N = 208 m = 102, f = 106		$p^{a)}$	N = 57 m = 31, f = 26		$p^{b)}$
	n (m/f)		n (m/f)[a)]			n (m/f)		
Apart from at school, how often does your child usually exercise so much that it gets out of breath or sweats?					0.024			<0.001
4–7 times/week	2	(1/1)	40	(25/15)		25	(15/10)	
2–3 times/week	7	(5/2)	106	(48/58)		24	(13/11)	
≤1 time/week	12	(6/6)	58	(27/31)		8	(3/5)	
Total	21		204			57		
At play and sports: *How is the child's endurance compared to its average peers?*					0.001			0.006
Equal	6	(3/3)	132	(60/72)		48	(25/23)	
Lower	16	(9/7)	74	(40/34)		9	(6/3)	
Total	22		206			57		
At play and sports: *How vigorous is the child compared to its average peers?*					0.003			0.012
More or equal	11	(8/3)	162	(76/86)		53	(28/25)	
Less	12	(5/7)	45	(25/20)		4	(3/1)	
Total	23		207			57		
How will you rate your child's proficiency in sports activities?					<0.001			<0.001
High	2	(2/0)	45	(19/26)		37	(23/14)	
Average	3	(2/1)	111	(57/54)		16	(6/10)	
Low	16	(8/8)	46	(23/23)		3	(2/1)	
Total	21		202			56		
How will you describe your child's manual dexterity compared to peers?					<0.001			0.001
Equal or better	7	(5/2)	157	(71/86)		55	(29/26)	
Clumsier	13	(7/6)	47	(29/18)		2	(2/0)	
Total	20		204			57		
How will you describe your child's gross motor function compared to peers?					<0.001			<0.001
Equal or better	5	(3/2)	142	(64/78)		54	(28/26)	
Clumsier	17	(10/7)	66	(38/28)		3	(3/0)	
Total	22		208			57		
Does your child participate in								
Team sports	8	(8/0)	100	(52/48)	0.225	41	(25/16)	0.002
Sports club activities other than team sports	4	(2/2)	68	(31/37)	0.133	16	(10/6)	0.506
Other organized activity	7	(5/2)	82	(32/50)	0.400	22	(10/12)	1.00

[a] Comparing EP/ELBW with or without neurodevelopmental disability (NDD).
[b] Comparing EP/ELBW without NDD and term born. χ^2-exact test.

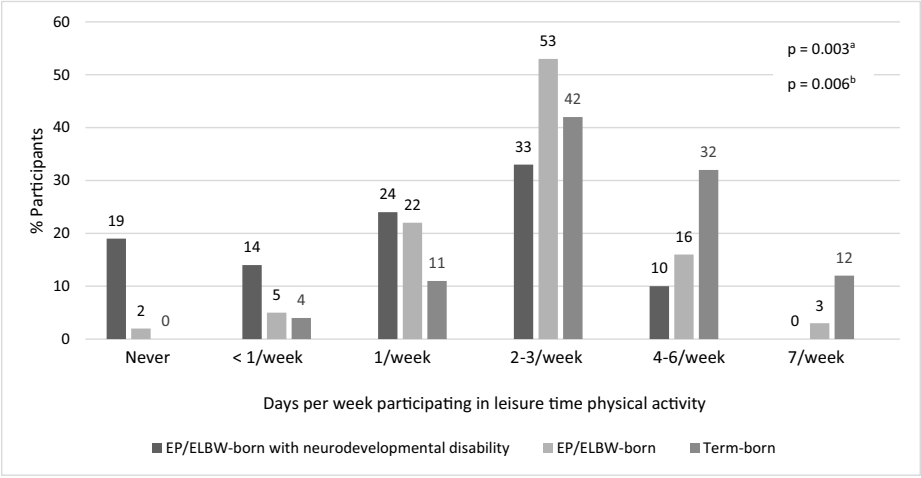

Fig. 2. Leisure time physical activity reported for the national cohort of children born extremely preterm/extremely low birthweight (EP/ELBW) with neurodevelopmental disability (n = 23), without neurodevelopmental disability (n = 208) and term-born controls (n = 57) born in Norway during 1999–2000.
p[a])Differences between the EP/ELBW children with and without neurodevelopmental disability. Exact chi-square test.
p[b])Differences between the EP/ELBW children without neurodevelopmental disability and the term-born children. Exact chi-square test.

Table 3
Prediction of reported reduced physical activity (PA) and clumsiness among 208 healthy children at 11 years of age born extremely preterm or with extremely low birthweight, by *the Movement Assessment Battery for Children*, *the Strength and Difficulties Questionnaire* reported as Total difficulty score and *The Wechsler Preschool and Primary Scale of Intelligence-Revised* assessment at the age of 5 years, using binary logistic regression.

Outcome at 11 years	Predictor: motor coordination problem at 5 years of age					
	Crude MABC5 (n = 21/170)			MABC5 adjusted		
	OR	95% CI	*p*	OR	95% CI	*p*
Leisure time PA ≤ 1 day/week	1.72	(0.64, 4.66)	0.283	1.33	(0.45, 3.90)	0.601[a]
Organized sports activities: not participating	1.97	(0.78, 4.97)	0.149	1.66	(0.61, 4.50)	0.320[a]
Lower endurance	2.66	(1.05, 6.72)	0.039	2.56	(1.00, 6.56)	0.051[b]
Less vigorous	5.41	(2.08, 14.11)	0.001	5.27	(2.00, 13.84)	0.001[b]
Poor proficiency in in sports activities	3.36	(1.23, 9.17)	0.018	2.95	(1.01, 8.67)	0.049[c+d]
Clumsy: manual dexterity	2.83	(1.06, 7.59)	0.038	1.21	(0.37, 3.94)	0.755[d+e]
Clumsy: gross motor function	3.40	(1.33, 8.65)	0.010	2.34	(0.85, 6.45)	0.101[d]

Outcome at 11 years	Predictor: behavioral problem at 5 years of age					
	Crude TDS90 (n = 46/153)			TDS90 adjusted		
	OR	95% CI	*p*	OR	95% CI	*p*
Leisure time PA ≤ 1 day/week	1.19	(0.54, 2.65)	0.668	1.09	(0.45, 2.14)	0.852[a]
Organized sports activities: not participating	2.35	(1.15, 4.81)	0.019	2.12	(0.97, 4.64)	0.060[a]
Lower endurance	2.57	(1.25, 5.30)	0.010	3.02	(1.41, 6.47)	0.004[b]
Less vigorous	3.21	(1.45, 7.12)	0.004	3.65	(1.60, 8.36)	0.002[b]
Poor proficiency in sports activities	3.90	(1.71, 8.90)	0.001	4.03	(1.62, 10.06)	0.003[c+d]
Clumsy: manual dexterity	2.19	(0.99, 4.83)	0.052	1.56	(0.624, 3.93)	0.339[d+e]
Clumsy: gross motor function	2.17	(1.05, 4.48)	0.036	1.18	(0.82, 4.16)	0.142[d]

Outcome at 11 years	Predictor: borderline intellectual functioning at 5 years of age					
	Crude FIQ 70–84 (n = 29/157)			FIQ 70–84 adjusted		
	OR	95% CI	*p*	OR	95% CI	*p*
Leisure time PA ≤ 1 day/week	1.44	(0.59, 3.50)	0.420	1.32	(0.51, 3.44)	0.570[a]
Organized sports activities: not participating	1.16	(0.49, 2.72)	0.736	0.98	(0.38, 2.49)	0.964[a]
Lower endurance	4.06	(1.73, 9.53)	0.001	4.19	(1.75, 10.05)	0.001[b]
Less vigorous	3.61	(1.50, 8.70)	0.004	3.60	(1.48, 8.75)	0.005[b]
Poor proficiency in in sports activities	2.11	(0.85, 5.24)	0.109	1.48	(0.55, 3.98)	0.434[c+f]
Clumsy: manual dexterity	3.06	(1.26, 7.40)	0.013	3.22	(1.22, 8.52)	0.019[e+f]
Clumsy: gross motor function	2.00	(0.88, 4.56	0.100	1.66	(0.70, 3.96)	0.253[f]

Abbreviations: FIQ: full-scale intelligence quotient according to The *Wechsler Preschool and Primary Scale of Intelligence-revised;* MABC: *Movement Assessment Battery for Children;* MABC5: MABC < the 5th percentile for age; TDS: Total difficulty score. TDS90: TDS ≥ the 90th percentile of the reference children.
Adjustments: a) low maternal education; b) use of asthma medication at 5 years of age; c) bronchopulmonary disease (oxygen dependency at 36 weeks postmenstrual age); d) borderline intellectual function (FIQ70–84); e) Small for gestational age; f) MABC5.

possible important impact of neuromuscular limitations on exercise capacity, studies exploring EP/ELBW children's trainability using custom made exercise programs could be useful.

5.2. Early predictors of physical activity among healthy EP/ELBW children

To our knowledge, this is the first study to investigate the predictive value of preschool minor motor-, behavioral- and intellectual deficits to estimate later physical activity among healthy-EP/ELBW school-children.

In our study, an abnormal MABC score at five years of age predicted poorer proficiency in sports activities and less vigorous PA at 11 years of age. This is in accordance with previous research, finding motor problems to persist and to become more apparent with increasingly demanding motor tasks as the child grows older [43,44]. Studies have shown that children with DCD have lower physical fitness, not solely explained by activity deficits [45,46], but possibly because they experience earlier fatigue than children who are more well-coordinated. However, the pathway linking DCD to reduced PA is not fully described, and psychosocial aspects may be significant. Children with DCD perceived themselves as less capable of exercise than their peers, and coping mechanisms may result in both withdrawing from arenas of PA and increased sedentary behavior [44,47,48].

EP/ELBW children have increased risk of behavioral problems and reduced cognitive function; features that are associated with motor coordination problems [49]. In the present study, an abnormal TDS (indicating behavioral problems) at five years of age predicted reduced endurance, less vigorous PA and poorer proficiency at sports activities at 11 years of age. Play and PA in childhood are demanding social activities requiring the ability to interact with peers and to interpret and adjust to feedback. Low self-esteem and reduced self-concept as well as inattention and hyperactivity all represent barriers to PA [44].

Reduced cognitive function has been linked to reduced level of aerobic and muscular fitness in children and adults [50,51]. We found that borderline intellectual functioning at five years of age predicted poorer manual dexterity, as well as lower endurance and less vigorous PA at 11 years of age. This may be explained by lack of motivation and opportunities for participation in PA as well as by DCD, which is known to be associated with lower intellectual functioning [33,51]. Improved exercise capacity has been associated with increased cognitive function [52]. How PA affects cognition is not fully explained, but research have shown that exercise may recruit use-dependent plasticity mechanisms

that prepare the brain to encode meaningful information from the environment and activate mechanisms that protect the brain from damage [53]. Thus, improving PA in EP/ELBW children might influence the individuals in ways that go beyond the physical effects.

Motor coordination, mental health and cognition all influence the preterm born child's ability to perform and participate in play and sports. In order to settle life-long healthy lifestyle habits, these children should actively be encouraged to take part in PA. The present study underlines the vulnerability of EP/ELBW schoolchildren with apparently mild problems. Preschool tests for motor coordination difficulties, behaviour problems or intellectual deficits could help direct parents and school personnel to facilitate PA during childhood in these children.

5.3. Strengths and limitations

The strengths of this study are the large population-based prospective design and the relatively high follow-up rate. However, several limitations need to be considered when interpreting the results. Firstly, we collected questionnaire-based data on physical activity rather than objective measurements like accelerometry (questions provided in Table 2). In addition, the behavioral problem assessment, the SDQ, relies solely on parental response, and no diagnostic tool were performed. The physiotherapists received formal training before study startup if they were not familiar with the MABC test, and experienced psychologists performed the WPPSI-R test. However, we did not perform a formal inter-rater agreement test specific for this study, and the test-personnel were not blinded for information on perinatal data.

The EP/ELBW children were recruited on the basis of either a GA of less that <28 weeks or BW of less than 1000 g irrespective of GA. Therefore, the results cannot be generalized to EP-born individuals in general. Also, the EP/ELBW children included at 11 years of age were probably healthier than the non-responding children, which influence the generalizability of our comparison between the term-born, healthy-EP/ELBW and the disabled EP/ELBW group. The term-born control-group was small, however based on the “next-born subject principle” for a subsample of the EP/ELBW cohort, reducing the risk of selection bias.

6. Conclusions

EP/ELBW schoolchildren had less favorable habits of physical activity than term-born children. In healthy-EP/ELBW children, subtle findings at five years of age regarding motor-, behavioral- and intellectual dysfunction, predicted lower proficiency and endurance and less vigorous physical activity at 11 years of age. This study suggests that information available at a very early age in these children can be used to design focused interventions to improve their habits of physical activity.

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Financial disclosure

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Data sharing statement

In accordance with the approvals granted for this study by The Regional Committee on Medical Research Ethics and The Norwegian Data Inspectorate, the data files are stored securely and in accordance with the Norwegian Law of Privacy Protection. The data file cannot be made publicly available as this might compromise the respondents' privacy. Some of the participating centres are small and the number of extremely preterm births limited with a risk of identifying anonymous participants. To prepare future research papers other researchers in our group currently use the data file. A subset of the data file with anonymized data can be made available to interested researchers upon reasonable request to Thomas Halvorsen (thomas.halvorsen@helse-bergen.no), providing Norwegian privacy legislation and GDPR are respected, and that permission is granted from The Norwegian Data Inspectorate and the data protection officer at Haukeland University Hospital.

CRediT authorship contribution statement

Mette Engan: Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing, Validation. **Merete Salveson Engeseth**: Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing, Validation. **Silje Fevang**: Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing, Validation. **Maria Vollsæter**: Methodology, Investigation, Data curation, Writing - original draft, Writing - review & editing, Validation. **Geir Egil Eide**: Supervision, Formal analysis, Data curation, Writing - review & editing, Validation. **Ola Drange Røksund**: Funding acquisition, Methodology, Investigation, Writing - review & editing, Validation. **Thomas Halvorsen**: Funding acquisition, Methodology, Investigation, Writing - review & editing, Validation. **Hege Clemm**: Resources, Conceptualization, Methodology, Writing - original draft, Writing - review & editing, Validation.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article to disclose.

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Appendix Table 1 Comparing neonatal characteristics, socioeconomic status, use of asthma medication, motor function (Motor Assessment Battery for Children (MABC)), intellectual function (*Wechsler Preschool and Primary Scale of Intelligence-revised)* and behavioral problems (*the Strength and Difficulties Questionnaire*) at 5 years to information on physical activity at 11 years of age among 208 healthy children born extremely preterm or with extremely low birthweight in the national cohort of Norway in 1999-2000

		PA≤ 1/week			Organized sports: not participating			Lower endurance			Less vigorous			Poor proficiency			Clumsy: manual dexterity			Clumsy: gross motor		
Variables, n		yes	no	p	yes	no	p	yes	no	p	yes	no	p	yes	no	p	yes	no	p	yes	no	p
Male gender	yes	27	73	0.756	31	71	0.555	40	60	0.249	25	76	0.317	23	76	1.00	29	71	0.067	38	64	0.103
	no	31	73		37	69		34	72		20	86		232	80		18	86		28	78	
Small for gestational age	yes	11	30	0.849	15	26	0.580	17	23	0.362	12	28	0.199	10	30	0.833	17	24	0.003	15	26	0.575
	no	47	116		53	114		57	109		33	134		36	126		30	133		51	116	
Bronchopulmonary dysplasia	yes	27	71	0.877	31	69	0.659	41	58	0.146	26	74	0.178	17	69	0.029	25	73	0.506	36	64	0.234
	no	31	75		37	71		33	74		19	88		29	87		22	84		30	78	
PDA surgical closure	yes	8	50	0.678	10	58	0.841	15	59	0.238	9	36	0.489	7	39	1.00	9	57	0.684	8	39	0.820
	no	24	122		23	117		18	114		24	138		24	132		24	118		24	133	
Asthma medication at 5 y	yes	9	27	1.00	12	25	1.00	18	19	0.030	11	26	0.176	11	25	0.099	11	25	0.165	16	21	0.110
	no	35	101		46	92		39	97		26	111		23	111		25	111		39	99	
Low maternal education	yes	22	35	0.032	23	35	0.088	24	34	0.183	15	43	0.330	11	46	0.704	11	46	0.305	21	37	0.400
	no	29	100		35	96		40	90		24	106		28	100		31	98		39	92	
MABC5	yes	7	13	0.410	10	11	0.216	11	10	0.045	11	10	0.001	8	11	0.020	8	12	0.043	12	9	0.012
	no	35	112		47	102		43	104		25	123		26	120		28	119		42	107	
TDS90	yes	12	34	0.682	22	24	0.025	22	23	0.014	17	28	0.005	17	28	0.001	15	31	0.058	28	20	0.036
	no	24	81		30	77		29	78		17	90		14	90		19	86		20	79	
FIQ70-84	yes	9	20	0.478	10	19	0.826	17	11	0.001	12	16	0.005	9	20	0.124	11	18	0.014	13	16	0.122
	no	30	96		40	88		35	92		22	106		22	103		21	105		37	91	

		MABC5			TDS90			FIQ70-84		
Variables, n		yes	no	p	yes	no	p	yes	no	p
Male gender	yes	15	71	0.061	24	51	0.725	18	61	0.217
	no	6	78		22	56		11	67	
Small for gestational age	yes	10	27	0.004	15	19	0.056	5	27	0.800
	no	11	122		31	88		24	101	
Bronchopulmonary dysplasia	yes	11	72	0.817	24	51	1.000	17	61	0.311
	no	10	77		22	56		12	67	
PDA surgical closure	yes	5	16	0.319	6	40	0.807	7	22	0.258
	no	20	129		17	90		18	110	
Asthma medication at 5 y	yes	6	30	0.396	7	23	0.389	7	27	0.803
	no	15	119		39	84		22	101	
Low maternal education	yes	9	42	0.193	19	30	0.052	12	33	0.008
	no	10	94		21	71		15	85	
MABC5	yes	-	-		10	7	0.011	9	10	0.002
	no	-	-		36	99		20	115	
TDS90	yes	10	36	0.011	-	-		17	23	< 0.001
	no	7	99		-	-		11	91	
FIQ70-84	yes	9	20	0.002	17	11	<0.001	-	-	-
	no	10	115		23	91		-	-	

Abbreviations: FIQ70-84: full scale IQ score of 70-84 point according to The *Wechsler Preschool and Primary Scale of Intelligence-revised;* MABC5: *Movement Assessment Battery for Children* < the 5th percentile for age*;* PA: physical activity PDA: patent ductus arteriosus; TDS90: Total difficulty score above the 90th percentile of the reference group, derived from *the Strength and Difficulties Questionnaire.* χ^2-exact test.

Additional information on the data collection

For children not participating at five years of age, but who did at 11 years of age (n = 35), results regarding neurodevelopmental disability (NDD) were obtained from the follow up at two years of age. None of these children had CP, were blind or deaf. Because intellectual disability could not be excluded by questionnaires for 18 of the 35 children, an experienced pediatrician contacted the parents of 17 children by phone. All parents considered their child to have a normal intellect. One participant, who did not attend examinations at two and five years of age but did participate at 11 years of age, was excluded from the analyses because of lack of information on NDD. One child without CP at examination at 5 years of age was moved from the health-EP/ELBW based on information obtained on reduced mobility at 11 years of age.

Paper III

frontiers in Pediatrics

ORIGINAL RESEARCH
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Left Vocal Cord Paralysis, Lung Function and Exercise Capacity in Young Adults Born Extremely Preterm With a History of Neonatal Patent Ductus Arteriosus Surgery—A National Cohort Study

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Background: Left vocal cord paralysis (LVCP) is a known complication of patent ductus arteriosus (PDA) surgery in extremely preterm (EP) born neonates; however, consequences of LVCP beyond the first year of life are insufficiently described. Both voice problems and breathing difficulties during physical activity could be expected with an impaired laryngeal inlet. More knowledge may improve the follow-up of EP-born subjects who underwent PDA surgery and prevent confusion between LVCP and other diagnoses.

Objectives: Examine the prevalence of LVCP in a nationwide cohort of adults born EP with a history of PDA surgery, and compare symptoms, lung function, and exercise capacity between groups with and without LVCP, and vs. controls born EP and at term.

Methods: Adults born EP (<28 weeks' gestation or birth weight <1,000 g) in Norway during 1999–2000 who underwent neonatal PDA surgery and controls born EP and at term were invited to complete questionnaires mapping voice-and respiratory symptoms, and to perform spirometry and maximal treadmill exercise testing. In the PDA-surgery group, exercise tests were performed with a laryngoscope positioned to evaluate laryngeal function.

Results: Thirty out of 48 (63%) eligible PDA-surgery subjects were examined at mean (standard deviation) age 19.4 (0.8) years, sixteen (53%) had LVCP. LVCP was associated with self-reported voice symptoms and laryngeal obstruction during exercise, not with lung function or peak oxygen consumption (VO_2peak). In the PDA-surgery group, forced expiratory volume in 1 second z-score (z-FEV_1) was reduced compared to EP-born controls ($n = 30$) and term-born controls ($n = 36$); mean (95% confidence interval) z-FEV_1 was −1.8 (−2.3, −1.2), −0.7 (−1.1, −0.3) and −0.3 (−0.5, −0.0), respectively.

For VO_2peak, corresponding figures were 37.5 (34.9, 40.2), 38.1 (35.1, 41.1), and 43.6 (41.0, 46.5) ml/kg/min, respectively.

Conclusions: LVCP was common in EP-born young adults who had undergone neonatal PDA surgery. Within the PDA-surgery group, LVCP was associated with self-reported voice symptoms and laryngeal obstruction during exercise, however we did not find an association with lung function or exercise capacity. Overall, the PDA-surgery group had reduced lung function compared to EP-born and term-born controls, whereas exercise capacity was similarly reduced for both the PDA-surgery and EP-born control groups when compared to term-born controls.

Keywords: infant: extremely premature, infant: extremely low birth weight, vocal cord paralysis, cohort studies, patent ductus arteriosus, ligation, bronchopulmonary dysplasia, exercise test

INTRODUCTION

Extreme preterm (EP) birth is associated with a number of perinatal complications causing short- and long-term morbidity (1, 2). A patent ductus arteriosus (PDA) is diagnosed in ∼40% of very low birth weight (<1,500 g) neonates and in 66% of EP-born neonates (3, 4). This shunt may give rise to cardiovascular dysfunction with pulmonary overcirculation and systemic hypoperfusion associated with worsening of lung disease, prolonged mechanical ventilation, increased risk of pulmonary hemorrhage, necrotizing enterocolitis, and intraventricular hemorrhage (5). Treatment options for PDA include a conservative symptomatic approach, pharmacological intervention, or surgical closure, the latter option usually representing a last resort (3, 6).

The left recurrent laryngeal nerve loops around the aorta in close proximity to the ductus arteriosus and left-sided vocal cord paralysis (LVCP) caused by iatrogenic nerve injury is a recognized complication of PDA surgery (7). Affected neonates may present with a weak cry, stridor, hoarseness, aspiration, and feeding problems (8, 9). Symptoms may be vague, and the condition can therefore pass unrecognized unless particularly examined for (10). Studies on EP-born neonates that report routine post-operative laryngoscopy have found incidences of LVCP ranging from 11 to 67% (7, 11).

Long-term consequences of LVCP in EP-born subjects beyond the first year of life are insufficiently described. A previous small study on EP-born adults who underwent neonatal PDA surgery discussed the possibility that LVCP occurring in the neonatal period may contribute to the long-term development of airway obstruction in this population (12), however, further research is needed on this topic. Moreover, both voice problems and breathing difficulties during physical activity could be expected with an impaired laryngeal inlet (13). More knowledge on long-term consequences of LVCP in the preterm population may prevent confusion between LVCP and other diagnoses with similar symptoms such as asthma or exercise-induced laryngeal obstruction (EILO).

As a group, premature infants who undergo PDA surgery may be particularly vulnerable to long-term health problems. PDA surgery has been associated with both bronchopulmonary dysplasia (BPD) and poor neurological outcomes (5, 8). Furthermore, several studies have found EP-born subjects to have reduced exercise capacity compared to term-born peers (14). We hypothesized that EP-born adults with a neonatal history of PDA surgery are at increased risk of impaired pulmonary and cardiorespiratory function, and that LVCP is associated with poorer outcomes.

We aimed to investigate the prevalence of LVCP in young adults born EP who underwent open PDA surgery in Norway during 1999–2000. Secondly, we aimed to compare self-reported voice and breathing symptoms, lung function, exercise capacity, and laryngeal obstruction during exercise between subjects with and without LVCP. Finally, we aimed to compare the lung function and exercise capacity in those who underwent PDA surgery with those of comparable EP-born controls and term-born controls.

METHODS

Subjects and Study Design

This was a nationwide observational follow-up study of all individuals born in Norway at gestational age (GA) <28 weeks or birth weight (BW) <1,000 gram during 1999–2000 (15). The inclusion process, data collection, and outcome at discharge from the neonatal intensive care unit (NICU) have been described in previous reports (16). PDA surgery was performed at four different hospitals. The indication for surgery was determined at the discretion of the neonatologists responsible for neonatal care and was based on clinical signs and echocardiographic evaluation.

The present study was conducted during 2018–2020, enrolling three groups (**Figure 1**):

(1) PDA-surgery: All individuals who had undergone neonatal PDA surgery and were enrolled in the nationwide cohort described above. This PDA-surgery group has two subgroups: those with and those without LVCP.
(2) EP-born controls: A regional sub-sample (Western Norway) of the same nationwide cohort from which the PDA-surgery group was recruited; however, with no history of neonatal PDA surgery.

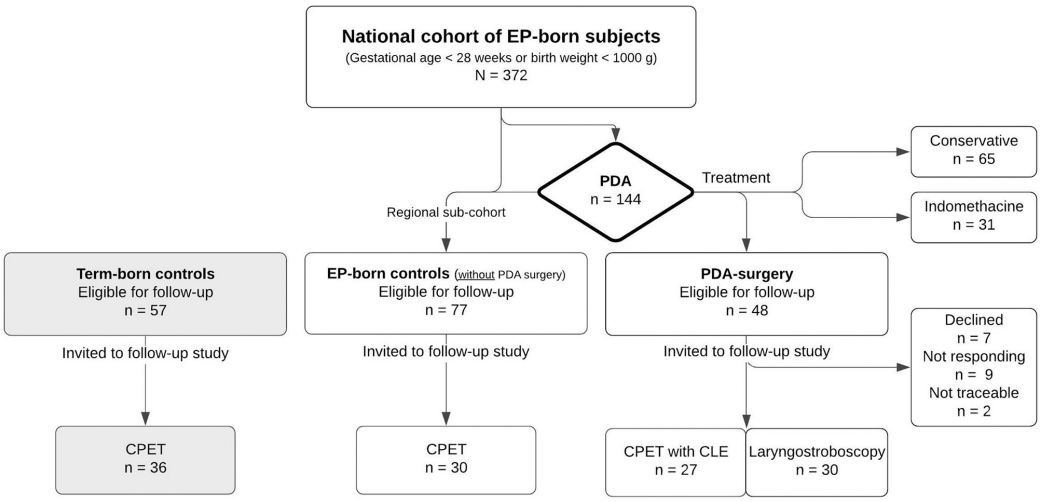

FIGURE 1 | Flow chart of the follow-up study of adults born extremely preterm with a neonatal history of patent ductus arteriosus surgery. CLE, continuous laryngoscopy exercise; CPET, cardiopulmonary exercise test; EP, extremely preterm (gestational age <28 weeks or birth weight <1,000 g); PDA: patent ductus arteriosus.

TABLE 1 | Early characteristics of the extremely preterm born adults enrolled in the national follow-up study on long-term consequences of neonatal patent ductus arteriosus surgery.

	PDA-surgery assessed		PDA-surgery not assessed			EP-born controls		
Characteristics	***n* = 30**		***n* = 18**		p^a	***n* = 30**		p^b
Female gender, *n* (%)	14	(47)	4	(22)	0.13	17	(57)	0.61
Birthweight, grams, mean (SD)[1]	792	(178)	781	(169)	0.83	845	(165)	0.24
Age of gestation, weeks, median (range)[2]	26	(23–29)	25	(23–27)	0.94	27	(24–31)	<0.001
Small for gestational age, *n* (%)	4	(13)	3	(17)	1.00	13	(43)	0.02
Prenatal steroids, *n* (%)	20	(67)	13	(72)	0.76	27	(90)	0.06
Surfactant, *n* (%)	27	(90)	18	(100)	0.28	24	(80)	0.47
Postnatal steroids, *n* (%)	20	(67)	14	(78)	0.52	8	(27)	0.004
Invasive ventilation, *n* (%)	29	(97)	17	(94)	1.00	25	(83)	0.20
Invasive ventilation, days, median (range)[2]	13	(1–87)	24	(1–52)	0.65	4	(1–21)	0.003
CPAP treatment, days, median (range)[2]	28.5	(0–92)	18	(4–58)	0.33	26	(0–72)	0.53
Patent ductus arteriosus, *n* (%)	30	(100)	18	(100)	1.00	11	(37)	<0.001
Age patent ductus arteriosus surgery, median (range)[2]	11	(4–34)	10	(2–36)	0.61	–	–	–
Bronchopulmonary dysplasia, *n* (%)	24	(80)	15	(83)	1.00	11	(37)	0.001
Normal neonatal cerebral ultrasound, *n* (%)	18	(60)	5	(28)	0.04	24	(80)	0.16

CPAP, continuous positive airway pressure; EP, Extremely preterm (gestational age <28 weeks or birthweight <1,000 g); PDA: patent ductus arteriosus. Bronchopulmonary dysplasia defined by oxygen supply and/or ventilatory support at gestational age 36 weeks. Prenatal steroids were recorded if given at least 24 h before delivery. Small for gestational age was defined as under the 10th percentile for gestational age (26). p) Fisher's exact test were used unless [1]independent t-test (equal variance not assumed) or [2]Mann-Whitney U-test is specified. [a]Differences between the group of subjects assessed and not assessed among those who had undergone PDA surgery; [b]Differences between the assessed PDA-surgery group and EP-born controls.

(3) Term-born controls: At 11 years of age, term born children were recruited as controls for the regional subsample of the EP-born children. The term born children were identified from birth protocols at the maternity ward and were invited as the next-born child of the same gender as the EP born child, with GA >37 weeks and BW >3,000 grams, corresponding to the Norwegian 10th-centile for BW.

TABLE 2 | Comparison of demographic and anthropometric variables between the groups of extremely preterm born subjects with- or without LVCP, EP-born controls and term-born controls.

			PDA-surgery					EP-born controls			Term-born controls			
	Total $n = 27$ (12 females)		LVCP $n = 14$ (5 females)		No LVCP $n = 13$ (7 females)			$n = 30$ (17 females)			$n = 36$ (13 females)			
Variables	Mean	SD	Mean	SD	Mean	SD	p^a	Mean	SD	p^b	Mean	SD	p^c	p^d
Age, years	19.4	0.7	19.3	0.7	19.5	0.8	0.40	20.4	1.0	<0.001	20.2	1.0	0.001	0.38
Height, *cm*	169.4	9.1	171.1	10.1	167.5	7.9	0.31	167.2	8.9	0.37	177.5	9.7	0.001	<0.001
Females	163.4	6.1	164.0	5.3	163.1	7.0	0.80	162.1	5.7	0.55	168.1	8.9	0.14	0.05
Males	174.1	8.4	175.1	10.1	172.8	5.6	0.58	173.9	7.9	0.95	182.8	5.0	<0.001	0.002
Weight, *kg*	63.8	12.7	65.5	12.4	61.9	13.2	0.47	65.4	16.5	0.68	73.7	14.7	0.006	0.04
Females	61.3	11.6	62.1	15.2	60.7	9.6	0.85	58.2	12.9	0.52	66.2	16.1	0.39	0.16
Males	65.8	13.5	67.4	11.0	63.4	17.4	0.63	74.8	16.3	0.13	77.9	12.3	0.009	0.55
BMI, kg/m^2	22.1	3.5	22.3	3.5	21.9	3.7	0.80	23.3	5.3	0.33	23.3	3.6	0.22	0.97
Females	22.8	3.4	22.9	4.7	22.7	2.5	0.92	22.2	5.4	0.75	23.2	4.0	0.78	0.58
Males	21.6	3.7	22.0	2.9	21.0	4.8	0.69	24.7	4.9	0.08	23.3	3.4	0.17	0.38

BMI, body mass index; EP, Extremely preterm (gestational age <28 weeks or birthweight <1,000 g); LVCP, left vocal cord paralysis; PDA, patent ductus arteriosus. p) Independent sample t-test (equal variance not assumed); [a]LVCP vs. no LVCP; [b]PDA-surgery group vs. EP-born controls; [c]PDA-surgery group vs. term-born controls; [d]EP-born controls vs. term-born controls.

Pulmonary Function

Vyntus® PNEUMO spirometer (Vyaire Medical GmbH, Leibnizstrasse, Hoechberg, Germany) was used to perform spirometry according to guidelines (17). Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1) and FEV_1/FVC were recorded. Raw data were transformed to z-scores using the reference equations of the Global Lung Function Initiative (18).

Cardiopulmonary Exercise Test

Peak exercise capacity was determined using a computerized incremental treadmill (Woodway PPS 55 Med, Weil am Rhein, Germany) exercise test according to a modified Bruce protocol (19) using a Vyntus CPX unit powered by SentrySuite software (Vyaire Medical GmbH, Hoechberg, Germany). Speed and elevation were increased every 90 s from an initial slow-walking phase. The test was stopped when the subject indicated severe exhaustion, preferably supported by a respiratory exchange ratio (RER) exceeding 1.05 or heart rate exceeding 95% of predicted maximal heart rate (20).

Variables of gas exchange and airflow were measured breath by breath and averaged over 10 s. The highest values for oxygen uptake determined during the last 60 s were recorded as peak values (VO_2peak). VO_2peak was reported as ml/kg/min and as the percentage of predicted using reference equations from a large sample of Norwegian subjects of relevant age (21). Exercise performance was described by the completed distance (meters) on the treadmill. The percentage inspiratory time to total time in a respiratory cycle (T_i/T_{tot}%) was used to describe the breathing pattern. Breathing reserve was the difference between maximal voluntary ventilation (FEV_1 x 35) and peak minute ventilation reported as the percentage of maximal voluntary ventilation.

Continuous Laryngoscopy Exercise (CLE) Test

CPET in the PDA-surgery group was performed with concomitant continuous transnasal flexible video-laryngoscopy (ENF TYPE V2, video processor CV-170, OLYMPUS, Tokyo, Japan) as described previously (22). LVCP was identified and later verified by laryngeal stroboscopy. The video recordings of the laryngeal inlet during treadmill running were assessed and rated for laryngeal obstruction according to a modified version of the classification described by Maat et al. (23). Because of laryngeal asymmetry in subjects with LVCP, a modified CLE-score (0–24 points) was developed, assessing the right and left glottic and supraglottic areas separately. The visually assessed medial rotation of the aryepiglottic folds and medialization of the vocal folds were scored ranging from normal (0 points) to maximal (3 points) at moderate (fast walking) and at maximal effort. The left and right sides were scored separately. The total modified CLE-score was the sum of the sub-scores at moderate and maximal exercise.

Questionnaires

All participants were asked to complete an online questionnaire mapping several health issues. The PDA-surgery group filled in

TABLE 3 | Self-reported respiratory- and voice symptoms between groups of adults born EP with- or without LVCP and EP-born controls.

	PDA-surgery				EP-born controls	
Symptoms	**LVCP** ***N*** **= 14**	**No LVCP** ***N*** **= 13**	**OP** ***N*** **= 3**	***p*** [a]	***N*** **= 23**	***p*** [b]
Hoarse voice, *n* (%)	8 (57)	1 (8)	3 (100)	0.01	3 (13)	0.09
Voice affects participation in singing, *n* (%)	8 (57)	1 (8)	3 (100)	0.01	–	
Voice that cracks when shouting, *n* (%)	7 (50)	2 (15)	3 (100)	0.10	–	
Weak or unclear voice which limits the possibility for being heard in a noisy environment, *n* (%)	8 (57)	4 (31)	3 (100)	0.25	–	
Voice affects participation in school-work or social activities, *n* (%)	4 (29)	3 (23)	3 (100)	1.00	–	
None of the symptoms above, *n* (%)	2 (14)	9 (69)	0 (0)	0.006	–	
Asthma medications last 12 months, *n* (%)	3 (21)	1 (8)	1 (33)	0.60	4 (17)	1.00
Breathing problems beyond normal during normal physical exertion, *n* (%)	9 (64)	6 (46)	3 (100)	0.45	7 (30)	0.09
"Scraping" sound or abnormal sounds during physical exertion, *n* (%)	6 (42)	2 (15)	2 (67)	0.21	2 (9)	0.09

EP, extremely preterm (gestational age <28 weeks and/or birthweight <1,000 g); LVCP, left vocal cord paralysis; OP, other pathology; PDA, patent ductus arteriosus. p) Fisher's exact test [a]LVCP vs. no LVCP; [b]PDA-surgery group (LVCP + no LVCP) vs. EP-born controls.

an additional paper-based questionnaire adapted from the Voice Handicap Index with questions regarding voice symptoms (24). The question on physical activity was adapted from the European Community Respiratory Health Survey II questionnaire (25). The questions "*Do you have breathing problems beyond normal during physical exertion*?" *Do you make scraping sounds or other abnormal sounds from the throat during physical exertion? Is your voice hoarser than in others of the same age?* and *"Does your voice affect participation in singing?"* were custom-made for the project.

Statistical Methods

Data were analyzed using the statistical software SPSS version 26 (IBM SPPS Statistics, NY, USA) and MedCalc version 19.5.3 (MedCalc Software Ltd, Osted, Belgium). Group comparisons were performed using the independent samples *t*-tests (equal variance not assumed) with 95% confidence intervals (95% CI), Mann-Whitney *U*-tests, or Fisher's exact tests, as appropriate. Analysis of covariance was used when the outcome for completed distance and VO_2peak was adjusted for gender and self-reported physical activity (hours of exercise per week) and to adjust for bronchopulmonary dysplasia (BPD) when comparing lung function variables between the PDA-surgery group and the EP-born control group. To examine whether the difference in VO_2peak between all EP-born and term-born controls differed by gender, an interaction term for gender and group affiliation was included. Linear regression with the modified CLE-score and gender as predictors was used to investigate whether VO_2peak was associated with the CLE-score after adjusting for gender. *P*-values ≤ 0.05 was characterized as statistically significant.

Ethics

The Regional Committee for Medical and Health Research Ethics in Western Norway approved the study. Informed written consents were obtained from all participants, or their parents if subjects were not competent to give consent.

RESULTS

Thirty of 48 (63%) eligible subjects in the nationwide PDA-surgery cohort consented to participate (**Figure 1**). One participant was unable to perform spirometry, and two were unable to run on the treadmill because of neurodevelopmental disability. Neonatal and demographic characteristics are given in **Tables 1**, **2**.

Left Vocal Cord Paralysis

In the PDA-surgery group, sixteen (53%) subjects were diagnosed with LVCP. Two subjects (7%) had laryngeal stenosis in addition to LVCP, and one subject (3%) presented right-sided arytenoid prolapse with overlying left-sided arytenoid fold making vocal cord assessment during phonation difficult, and LVCP could therefore not be determined (these three subjects are referred to as *other pathology* and they were excluded from further analysis). Thirteen subjects (43%) had a normal laryngeal exam (no LVCP or major anatomic pathology). One subject with LVCP and all three subjects with *other pathology* were aware of their laryngeal pathology before entering this study, the remaining 12 were not. Within the PDA-surgery group, those with LVCP had more often received postnatal steroids compared to those with a normal larynx, whereas other neonatal characteristics were similar (**Supplementary File**).

Only 14% of those with LVCP compared to 69% of those without LVCP reported no voice-related symptoms ($p = 0.006$) (**Table 3**). Around 50% reported abnormal sounds from the throat and breathing problems during physical exertion, with no differences between the groups with and without LVCP. All three subjects with *other pathology* reported voice symptoms and breathing problems during physical exertion.

TABLE 4 | Comparison of spirometry results between groups of adults born EP with- or without LVCP, EP-born controls and term-born controls.

	PDA-surgery							EP-born controls			Term-born controls			
	Total N = 26 (12 females)		LVCP n = 13 (5 females)		No LVCP n = 13 (7 females)			n = 30 (17 females)			n = 36 (13 females)			
Variables	Mean	95%CI	Mean	95%CI	Mean	95%CI	p^a	Mean	95%CI	p^b	Mean	95%CI	p^c	p^d
FVC, *L*	4.11	3.68, 4.55	4.32	3.67, 4.97	3.90	3.26, 4.55	0.34	4.32	3.95, 4.68	0.46	5.17	4.80, 5.53	<0.001	0.001
FVC, *z-score*	−0.92	−1.44 to −0.40	−0.80	−1.35 to −0.25	−1.05	−2.02, 0.07	0.64	−0.16	−0.49 to 0.18	0.02	−0.10	−0.32 to 0.12	0.005	0.77
FEV_1, *L*	3.10	2.76, 3.44	3.25	2.69, 3.80	2.96	2.49, 3.42	0.39	3.49	3.21, 3.76	0.08	4.31	4.03, 4.59	<0.001	<0.001
FEV_1, *z-score*	−1.76	−2.31 to −1.21	−1.79	−2.52 to −1.06	−1.73	−2.68 to −0.79	0.92	−0.68	−1.07 to 0.29	0.002	−0.28	−0.51 to −0.04	<0.001	0.08
FEV_1/FVC ratio	0.76	0.72, 0.80	0.75	0.69, 0.82	0.77	0.71, 0.83	0.74	0.81	0.79, 0.84	0.03	0.84	0.82, 0.86	<0.001	0.17
FEV_1/FVC, z-score	−1.50	−2.01 to −0.98	−1.52	−2.36 to −0.68	−1.47	−2.19 to −0.74	0.92	−0.81	−1.20 to −0.42	0.03	−0.36	−0.61 to −0.11	<0.001	0.06

EP, Extremely preterm (gestational age <28 weeks or birthweight <1,000 g); FEV_1: forced expiratory in 1 s; FVC, forced vital capacity; LVCP: left vocal cord paralysis; PDA: patent ductus arteriosus; 95%CI: 95% confidence interval. p) Independent sample t-test (equal variance not assumed); [a]LVCP vs. no LVCP; [b]PDA-surgery group vs. EP-born controls; [c]PDA-surgery group vs. term-born controls; [d]EP-born controls vs. term-born controls.

Lung Function

The three participants with *other pathology* were excluded from the analyses of lung function and exercise capacity. Within the PDA-surgery group, we did not find statistically significant differences in spirometry values between subjects with or without LVCP. However, clinically relevant differences could not be excluded given the wide the confidence intervals (**Table 4**).

The PDA surgery group had reduced z-FVC, z-FEV_1, and z-FEV_1/FVC, compared to the EP-born controls and the term-born controls (**Table 4**; **Figure 2**; **Supplementary File**). Neonatal BPD was present in 80% of the PDA-surgery group and in 37% of the EP-born controls, and BPD was associated with reduced z-FVC and z-FEV_1. Adjusting for BPD, z-FEV_1 was still significantly lower in the PDA-surgery group compared to the EP-born group with a mean (95%CI) difference of 0.89 (1.17, 1.61), $p = 0.02$.

Exercise Capacity

All participants ran to perceived maximal exhaustion and all achieved RER above 1.05 or heart rate above 95% predicted. Within the PDA-surgery group, we did not find statistically significant differences in completed distance, VO_2peak (ml/kg/min as well as the percentage of predicted), or self-reported physical activity for subjects with and without LVCP (**Table 5**; **Supplementary File**). However, clinically relevant differences could not be excluded given the wide confidence intervals. T_i/T_{tot}% was higher in the participants with LVCP compared to those without LVCP, and also higher than in the EP-born controls and the term-born controls. Mean (95% CI) difference between those with LVCP vs. all the other groups combined was 2.8% (1.6, 4.1) $p < 0.001$.

The PDA-surgery group had similar exercise capacity and self-reported physical activity as the EP-born control group. All EP-born participants combined (PDA-surgery and EP-born controls), ran a shorter distance, had lower VO_2peak (ml/kg/min), and reported less physical activity compared to term-born controls (**Table 5**; **Figures 2**, **3**; **Supplementary File**). Adjusted for gender, mean (95% CI) difference in completed distance and VO_2peak between all the EP-born participants combined vs. the term-born controls was 218 (114, 322) meters, $p < 0.001$, and 4.9 (1.8, 8.0) ml/kg/min, $p = 0.002$, respectively. There was no significant interaction effect between gender and group affiliation (all EP-born and term-born) on VO_2peak ($p = 0.16$). After additional controlling for physical activity, the completed distance on the treadmill was still shorter for EP-born participants compared to the term-born control group [mean (95% CI) difference 150 (39, 260) meters, $p = 0.009$]. Moreover, VO_2peak difference was slightly reduced [3.2 (−0.2, 6.7) ml/kg/min] and no longer statistically significant ($p = 0.07$).

Continuous Laryngoscopy Exercise Findings (PDA-Surgery Participants Only)

In the PDA-surgery group, 27/30 participants performed a CLE test. Among these, the modified CLE-score at moderate and maximal effort could not be determined in three subjects, and the

TABLE 5 | Comparison of cardiopulmonary exercise measures in the group of adults born EP with- or without LVCP, EP-born controls and term-born controls.

	PDA-surgery							EP-born controls			Term-born controls			
	Total *N* = 25 (12 females)		LVCP *n* = 13 (5 females)		No LVCP *n* = 12 (7 females)			*n* = 30 (17 females)			*n* = 36 (13 females)			
CPET variables	**Mean**	**95%CI**	**Mean**	**95%CI**	**Mean**	**95%CI**	p^a	**Mean**	**95%CI**	p^b	**Mean**	**95%CI**	p^c	p^d
Peak heart rate, *beat/min*	191	185, 197	191	181, 201	191	183, 199	0.98	193	190, 196	0.54	195	191, 198	0.27	0.43
RER at peak exercise, units	1.24	1.21, 1.28	1.22	1.16, 1.27	1.27	1.22, 1.31	0.16	1.27	1.23, 1.30	0.24	1.26	1.24, 1.28	0.36	0.65
Ti/Ttot, %	51.0	49.9, 52.1	52.4	51.2, 53.6	49.4	47.8, 51.0	0.004	49.7	48.7, 50.7	0.09	49.5	48.6, 50.3	0.03	0.75
Breathing reserve, %	17	11, 23	20	13, 28	13	3, 23	0.19	16	11, 22	0.93	11	6, 16	0.12	0.11
Peak respiratory rate, *breaths/min*	46	42, 50	43	38, 48	49	42, 55	0.13	48	44, 51	0.47	54	50, 58	0.003	0.01
Females	47	41, 53	44	35, 53	50	40, 60	0.27	46	42, 51	0.76	51	45, 57	0.36	0.19
Males	44	39, 50	43	35, 50	47	34, 61	0.42	49	44, 54	0.18	56	50, 61	0.004	0.06
Peak minute ventilation, *L/min*	89	74, 99	90	74, 105	89	75, 103	0.94	101	92, 110	0.07	134	123, 144	<0.001	<0.001
Females	77	67, 86	72	51, 93	80	66, 94	0.43	90	80, 99	0.07	102	93, 110	<0.001	0.03
Males	101	86, 115	101	80, 121	101	68, 135	0.95	118	106, 129	0.06	152	141, 162	<0.001	<0.001
Distance, *meter*	892	805, 978	935	783, 1,086	835	779, 890	0.19	858	763, 953	0.59	1,117	1,017, 1,216	0.001	<0.001
Females	856	627, 1,084	932	305, 1,558	780	682, 878	0.50	777	667, 887	0.49	917	810, 1,024	0.59	0.06
Males	914	840, 988	936	809, 1,063	879	820, 937	0.35	964	801, 1,127	0.55	1,230	1,104, 1,355	<0.001	0.01
Peak VO_2, *ml/kg/min*	37.5	34.9, 40.2	38.5	33.6, 43.4	36.5	33.9, 39.0	0.43	38.1	35.1, 41.1	0.76	43.6	41.0, 46.5	0.002	0.007
Females	35.8	31.0, 40.5	38.1	23.9, 52.3	34.1	31.8, 36.4	0.48	36.4	32.6, 40.2	0.82	38.5	35.0, 42.0	0.32	0.40
Males	39.2	36.1, 42.3	38.8	33.7, 43.9	39.8	35.6, 44.0	0.70	40.4	35.2, 45.5	0.67	46.6	43.3, 49.9	0.001	0.04
Peak VO_2, *% of predicted*	79.6	73.5, 85.8	80.3	68.1, 92.4	79.0	74.9, 79.3	0.83	83.1	76.5, 89.6	0.44	90.2	85.5, 94.9	0.007	0.08
Females	85.0	73.6, 96.4	90.6	56.3, 124.9	81.0	75.5, 86.6	0.49	87.4	78.1, 96.6	0.73	92.2	83.9, 100.4	0.28	0.41
Males	74.7	68.8, 80.5	73.8	64.1, 83.5	76.1	68.3, 83.9	0.65	77.4	67.8, 87.1	0.60	89.1	82.9, 95.3	0.001	0.04

CPET, cardiopulmonary exercise test; EP, Extremely preterm (gestational age <28 weeks and/or birthweight <1,000 g); LVCP, left vocal cord paralysis; PDA, patent ductus arteriosus; RER, respiratory exchange ratio; Ti/Ttot, Inspiratory time/Total inspiratory and expiratory time ratio; VO_2, oxygen consumption; 95% CI, 95% confidence interval. Breathing reserve is the difference between maximal voluntary ventilation (FEV_1 x 35) and peak minute ventilation reported as the percentage of maximal voluntary ventilation. (p) Independent sample t-test (equal variance not assumed); [a]LVCP vs. no LVCP; [b]PDA-surgery group vs. EP-born controls; [c]PDA-surgery group vs. term-born controls; [d]EP-born controls vs. term-born controls.

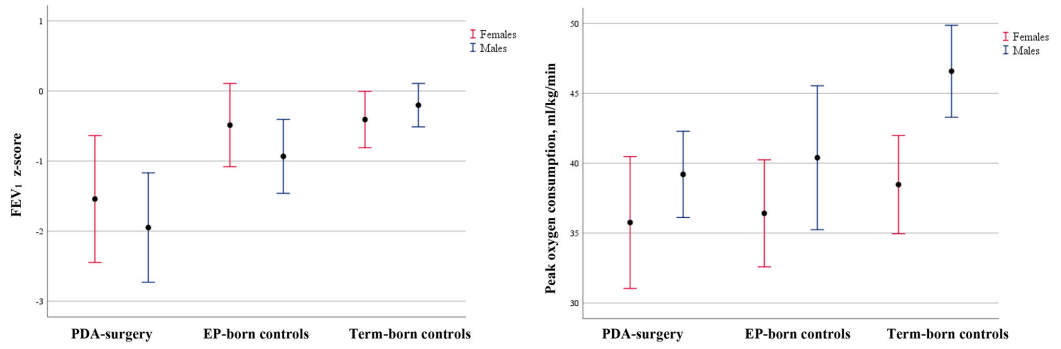

FIGURE 2 | Comparison of lung function and oxygen consumption between EP adults who underwent neonatal patent ductus arteriosus surgery, EP-born controls, and term-born controls. Error bars of mean with 95% CI for FEV_1 z-score and peak oxygen consumption (ml/kg/min) for the PDA-surgery group, EP-born controls, and term-born controls stratified by gender. *Abbreviations*: EP: extremely preterm (gestational age <28 weeks and/or birth weight <1,000 g); PDA: patent ductus arteriousus.

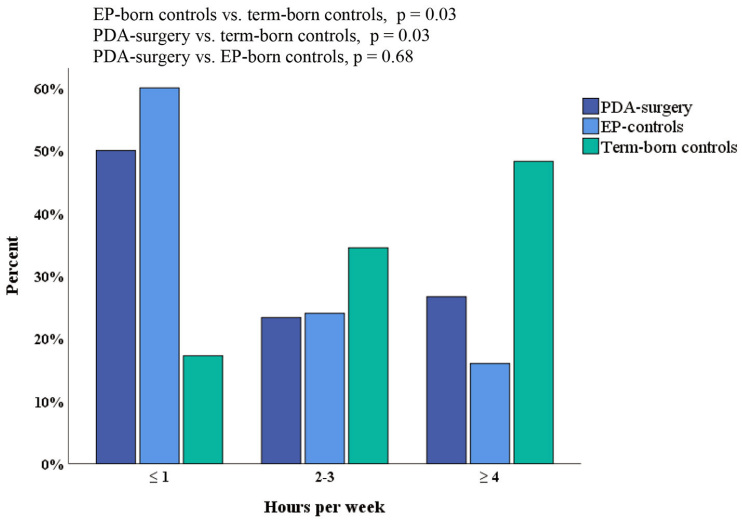

FIGURE 3 | Self-reported physical activity among the EP-born participants who underwent neonatal PDA surgery, EP-born controls and term-born controls. Answer to the self-reported question *"How many hours per week do you attend sports, exercise, or exert yourself so much that you get out of breath and/or sweat?"* Response rate: PDA-surgery: $n = 30/30$, EP-born controls: $n = 25/30$, Term-born controls: $n = 29/36$ p) Chi-square test. EP, extremely preterm (gestational age <28 weeks and/or birth weight <1,000 g); PDA, patent ductus arteriousus.

total score was derived from the sub-scores at rest and maximal effort, or at rest and moderate effort.

In the group with LVCP, all but one had a modified CLE-score >4, indicating laryngeal obstruction during exercise. In those with no LVCP, only three subjects had a modified CLE-score >4 (**Figure 4**), which suggests they had the specific diagnosis of EILO as all had normal larynx at rest (27). **Figure 5** demonstrates the laryngeal inlet in three participants, one with a normal larynx and two with LVCP.

The group of subjects reporting breathing difficulties during exercise and those reporting abnormal sounds from the throat during exercise did not have a higher modified CLE-score than those without these symptoms (**Supplementary File**). Furthermore, the modified CLE-score was not associated with VO_2peak after adjusting for gender ($p = 0.40$).

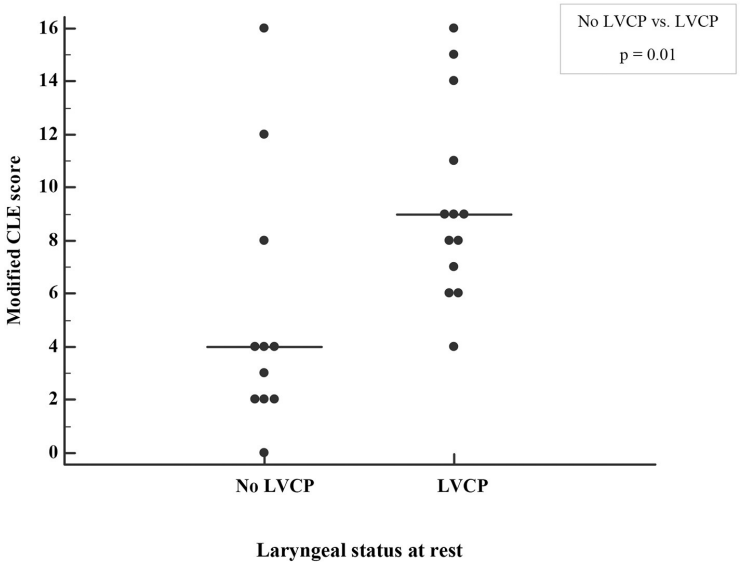

FIGURE 4 | Laryngeal obstruction during exercise graded by a modified continuous laryngoscopy exercise (CLE) score in the adults born EP with or without left vocal cord paralysis (LVCP). The median CLE-scores are indicated by horizontal lines. p) Mann-Whitney *U*-test.

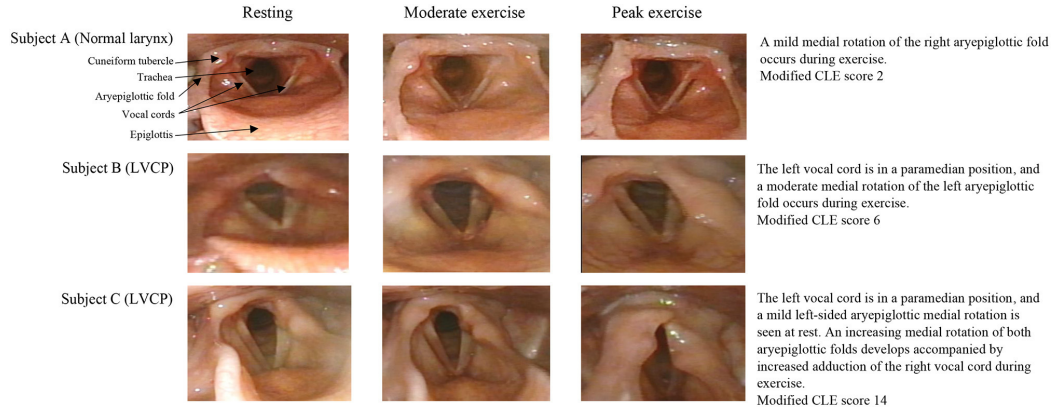

FIGURE 5 | Images of the larynx during exercise in EP-born individuals who had undergone neonatal PDA surgery.

DISCUSSION

This is the first study to report the prevalence of LVCP in a national cohort of young adults with a history of EP birth and surgical closure of PDA during their neonatal period. Within the PDA-surgery group, more than half of the participating subjects were diagnosed with LVCP, which was associated with characteristic voice symptoms, prolonged inspiratory to total respiratory time, and laryngeal obstruction during exercise. We did not find an association between LVCP and lung function or exercise capacity, however, the power to detect such associations was low due to the limited sample size. Overall, the PDA-surgery group had impaired lung function compared to EP-born as well as term-born controls, whereas exercise capacity was similarly reduced for both PDA-surgery and EP-born controls compared to term-born controls.

Studies examining LVCP after PDA surgery in EP-born neonates have mainly been performed in the immediate postoperative period or during infancy (28). Our group has previously identified LVCP in 7 of 11 EP-born adults

participating in a small local cohort study (12). In this national study, the prevalence of LVCP was 53%, compared to the 32% reported in a meta-analysis of studies examining all infants after PDA surgery (28). Performing laryngeal examinations on neonates is challenging, and pathology may be overlooked (29). This may explain the high prevalence of LVCP in studies assessing adults who are easier to examine. We do not have complete information on whether clips or ligature were used for PDA closure; hence, we could not assess a possible influence from the mode of surgery.

Dysphonia is a known long-term complication of preterm birth and is associated with extreme prematurity, emergency intubations, and multiple intubations, as well as PDA surgery (13, 30, 31). Unilateral vocal cord paralysis is associated with social and physical limitations and reduced health-related quality of life (32). There were more reports of voice symptoms in the subjects with LVCP; however, about one-third of subjects without LVCP also reported voice symptoms. Several of the subjects with LVCP in our study reported that their voice affected their participation in singing, social activities, and schoolwork. Surgical treatment and voice therapy may improve voice quality, and we encourage that a laryngeal examination is performed after neonatal PDA surgery (33).

Local traumas related to intubation and prolonged time on invasive mechanical ventilation are known risk factors for laryngeal injury (34). We found that 3/30 (10%) of the participants who underwent laryngoscopy had major laryngeal pathology other than LVCP. All three reported voice symptoms and breathing problems during exercise and all were aware of their malfunctioning larynx prior to study enrollment, contrasting the participants with LVCP, where only one had been aware of their pathology in advance. This certainly underlines the importance of suspecting laryngeal pathology in EP-born individuals with voice or respiratory complaints and to include an upper airway assessment to achieve a comprehensive understanding of their symptoms.

BPD and PDA

In the PDA-surgery group in this present study, more had BPD and the lung function was poorer in adulthood, compared to the EP-born control group. There is convincing evidence that preterm-born survivors with or without BPD have an increased risk for poor adult lung function (35). The association between PDA surgery and BPD has been reported earlier (8, 36), and may be explained by more severe neonatal respiratory illness, as PDA surgery tends to be performed as "rescue therapy" in infants with already advanced lung disease and/or failed pharmacological treatment of PDA (5, 37). However, population-based observational studies have suggested that early surgical ligation is an independent risk factor for BPD (38, 39). A re-examination of the only randomized controlled trial investigating the effects of prophylactic PDA ligation vs. delayed ligation revealed a significant increase in BPD incidence in those who were ligated prophylactically (40). Animal studies support a link between PDA ligation and the development of chronic lung disease by increased expression of genes involved in pulmonary inflammation and decreased alveolar fluid clearance (41). However, these issues are incompletely understood.

Exercise Capacity, Physical Activity, and Laryngeal Obstruction During Exercise

In individuals with LVCP, the para-median position of a paralyzed left vocal cord would be expected to interfere with the normal exercise-induced dilation of the glottis, and thus potentially compromise airflow capacity and exercise capacity. We found that subjects with LVCP had prolonged inspiration and a tendency for a lower peak respiratory rate at peak exercise. By laryngoscopy, we observed severe laryngeal obstruction during exercise in several individuals affected with LVCP (**Figure 5**). However, LVCP and the modified CLE-score were not associated with VO_2peak. This finding is in line with our previous study, where no association between VO_2peak and LVCP was found in EP-born adults (12). The results from these two studies suggest that it is possible to obtain average exercise capacity despite a relatively severe laryngeal obstruction.

A number of long-term sequelae of EP birth may affect subsequent exercise capacity, such as cardiopulmonary and neuromuscular impairment, reduced skeletal muscle mass, and behavioral issues such as less participation in physical activity (2). A review of 22 studies on exercise capacity concluded that children and adults born preterm have 13% lower VO_2peak (ml/min/kg) than term-born, in line with the ∼11% (-4.9 ml/kg/min) lower VO_2peak observed for all our EP-born participants combined (14). Similar to previous reports, we found that a lower amount of physical activity may be an explanatory factor for the relatively modest deficit in VO_2peak (42). It is still not determined if an increased level of physical activity will lead to improved exercise capacity in EP-born adults. Morales Mestre et al. conducted a randomized intervention study on EP-born children diagnosed with BPD and found that a structured exercise program improved exercise capacity (43). We encourage more research to be invested in this area to expand the knowledge on participation in physical activity and trainability in the EP-born population.

Strengths and Limitations

The strengths of this study were a population-based design with several centers responsible for the PDA surgery, and a high rate of participation. It was a limitation that only the PDA-surgery group was examined with laryngoscopy. Undiscovered LVCP or other laryngeal pathology might have been present in the EP-born control group, due to e.g., pressure from a large PDA or a large pulmonary trunk (44). Furthermore, laryngoscopy was not performed in the neonatal period and preoperative pathology or spontaneous postoperative improvement of LVCP could not be assessed. Cardiopulmonary exercise data for the PDA-surgery group were obtained from CLE-tests, which we have shown can be used interchangeably with data obtained from a regular CPET (22). Information on physical activity was self-reported and not determined by a more objective method like accelerometry or diary. Furthermore, the question on physical activity did not include aspects of mode and intensity, factors that may have affected the correlation between VO_2peak and physical activity.

The number of eligible subjects was determined by the number of EP-born infants who underwent PDA surgery in Norway during 1999–2000. The sample size was relatively small with large variation within the groups, resulting in a reduced

power to detect differences in the subgroup analyses. About one-third of the eligible EP-born adults who had undergone PDA surgery were lost to follow-up (**Figure 1**). Recruiting young adults with a busy schedule is challenging and individuals with voice or breathing symptoms might have been more motivated to participate than individuals without such symptoms. The estimated prevalence of LVCP in this cohort lies within the range of 16/48 (33%) to 34/48 (71%) if no one or all non-participating subjects were diagnosed with LVCP. Furthermore, the study protocol requested treadmill running which might have motivated those able to and familiar with running to participate. More subjects in the participating group had a normal neonatal cerebral ultrasound compared to the non-participating group, implying a selection of subjects with less neurological sequela (**Table 1**).

Management of PDA in EP-born individuals is still under debate (45). Reports suggesting associations with negative post-operative outcomes have contributed to a decline in the rate of PDA surgery in the last decade (46). However, selection by indication represents a challenge and may not have been fully accounted for when reporting on outcomes (5, 47). Choice of surgical procedure may also affect outcomes. Surgical ligation has been associated with higher rates of LVCP than surgical clipping (48). Unfortunately, we did not have complete information on surgical methods in our data set. New catheter-based procedures add options for PDA closure also for infants <1,000 g (49). Irrespective of future guidelines for PDA management, a population of EP-born subjects with a history of neonatal PDA surgery already exists. Therefore, clinicians caring for EP-born children and adults should be aware of symptoms and long-term outcomes associated with PDA-surgery and LVCP to ensure proper follow-up.

CONCLUSIONS

In this nationwide study, LVCP was present in 53% of EP-born young adults who had undergone neonatal PDA surgery. Within the PDA-surgery group, LVCP was associated with self-reported voice symptoms and laryngeal obstruction during exercise. We did not find an association between LVCP and lung function and exercise capacity, however; the power to detect such associations was low. Overall, the PDA-surgery group had impaired lung function compared to EP-born and term-born controls, whereas exercise capacity was similarly reduced for both PDA-surgery and EP-born controls compared to term-born controls.

Clinicians caring for EP-born children and adults should be aware of possible laryngeal sequelae after PDA surgery. Furthermore, EP-born subjects with a history of PDA surgery represent a population that needs follow-up to monitor lung function. Despite a high-risk start to life, EP-born individuals who underwent PDA surgery seem to achieve an exercise capacity only modestly decreased compared to term born individuals.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because in accordance with the approvals granted for this study by the Regional Committee on Medical Research Ethics and the Norwegian Data Inspectorate, the data files are stored securely and in accordance with the Norwegian Law of Privacy Protection. The data file cannot be made publicly available as this might compromise the respondents' privacy. Some of the participating centers are small and the number of extremely preterm births is limited with a risk of identifying anonymous participants. A subset of the data file with anonymized data can be made available to interested researchers upon reasonable request, providing Norwegian privacy legislation and GDPR are respected, and that permission is granted from The Norwegian Data Inspectorate and the data protection officer at Haukeland University Hospital. Requests to access the datasets should be directed to Maria Vollsæter, maria.vollseter@helse-bergen.no.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Regional Committees for Medical and Health Research Ethics West, The University of Bergen, 5021 Bergen, Norway. Informed written consents were obtained from all participants, or their parents if subjects were not competent to give consent.

AUTHOR CONTRIBUTIONS

ME and MSE have coordinated and collected data, organized data, carried out the analyses, drafted the initial manuscript, and revised the manuscript. MV has designed the data collection instruments, collected and organized data, and has reviewed and revised the manuscript. LS, OG, and IE have collected and organized data and critically reviewed the manuscript for important intellectual content. KH has given advice on the analysis of data, participated in the interpretation of the data, and critically reviewed the manuscript for important intellectual content. KØ, OR, and TH have provided funding, designed the data collection instruments, coordinated and supervised data collection, and have critically reviewed the manuscript for important intellectual content. HC has conceptualized and designed the study, designed the data collection instruments, drafted the initial manuscript, and has critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2021.780045/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary Material

Supplementary table 1 Neonatal characteristics of the enrolled extremely preterm born adults who had undergone patent ductus arteriosus surgery

Characteristics	**PDA-surgery**						
	LVCP n = 14		No LVCP n = 13		Other pathology n = 3		*p*
Female gender, *n (%)*	5	(36)	7	(54)	2	(67)	0.45
Birthweight, *grams, mean (SD)* [1)]	767	(174)	820	(197)	786	(144)	0.47
Age of gestation, *weeks, median (range)*[2)]	25	(23-27)	26	(23-29)	25	(24-26)	0.32
Small for gestational age, *n (%)*	2	(14)	2	(8)	0	(0)	1.00
Prenatal steroids, *n (%)*	9	(64)	9	(69)	2	(67)	1.00
Surfactant, *n (%)*	13	(93)	12	(92)	2	(67)	1.00
Postnatal steroids, *n (%)*	12	(86)	5	(38)	3	(100)	0.02
Invasive ventilation, *n (%)*	14	(100)	12	(92)	3	(100)	0.48
Invasive ventilation, days, *median (range)* [2)]	15	(1-85)	10	(2-87)	17	(15-83)	0.30
CPAP treatment, days, *median (range)* [2)]	32.5	(0-92)	27	(2-58)	31	(23-50)	0.58
Age PDA surgery, *median (range)* [2)]	7.5	(4-31)	11	(4-35)	23	(11-27)	0.31
Bronchopulmonary dysplasia, *n (%)*	12	(86)	10	(77)	2	(67)	0.65
Normal cerebral ultrasound, *n (%)*	7	(50)	9	(69)	2	(67)	0.44

Abbreviations: CPAP: continuous positive airway pressure; EP: extremely preterm (gestational age < 28 weeks or birthweight < 1000 g); LVCP: left vocal cord paralysis; OP: other pathology; PDA: patent ductus arteriosus.

Bronchopulmonary dysplasia defined by oxygen supply and/or ventilatory support at gestational age 36 weeks. Small for gestational age was defined as under the 10th percentile for gestational age. Prenatal steroids were recorded if given at least 24 hours before delivery.

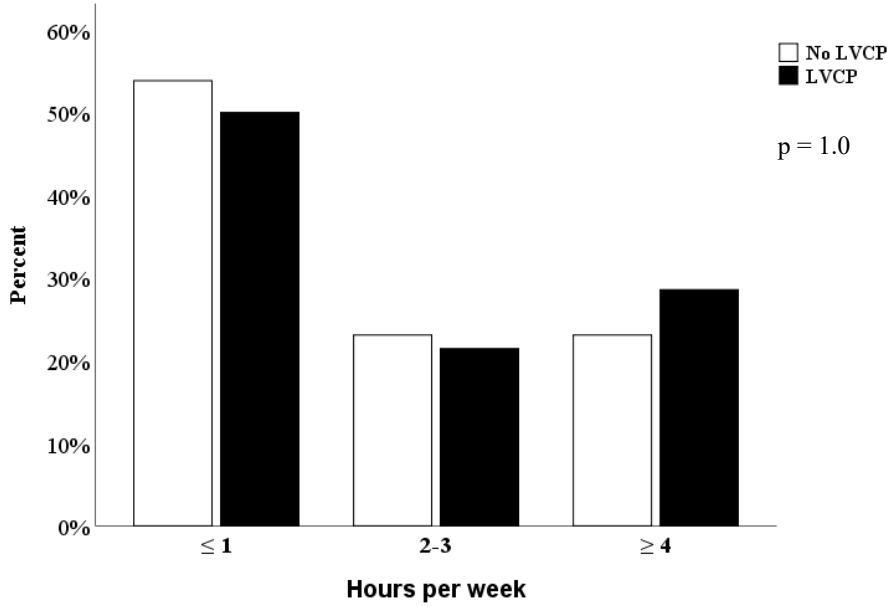
p) Fisher's exact test were used unless 1) independent t-test (equal variance not assumed) or 2) Mann-Whitney U test is specified.

Supplementary table 2 Differences in lung function and cardiopulmonary exercise measures between the group of young adults born EP with- or without LVCP, EP-born controls and term-born control

	Within PDA-surgery group: LVCP vs. no LVCP			**PDA-surgery group vs. EP-born controls**			**PDA-surgery group vs. term-born controls**			**EP-born controls vs. term-born controls**		
Spirometry variables	Mean diff	95%CI	p	Mean diff	95%CI	p	Mean diff	95%CI	p	Mean diff	95%CI	p
FVC, *z-score*	0.24	-0.83, 1.32	0.64	-0.77	-1.37, -0.16	0.02	-0.83	-1.39, -0.27	0.005	-0.06	-0.45, 0.34	0.77
FEV_1, z-score	-0.06	-1.19, 1.08	0.92	-1.08	-1.75, -0.42	0.002	-1.48	-2.08, -0.89	<0.001	-0.40	-0.85, 0.05	0.08
FEV_1/FVC, z-score	-0.05	-1.10, 1.00	0.92	-0.69	-1.32, -0.05	0.03	-1.14	-1.70, -0.57	<0.001	-0.45	-0.91, 0.01	0.06
CPET variables												
Peak heart rate, *beat/min*	0.2	-12.3, 12.6	0.98	-2.0	-8.8, 4.7	0.54	-3.9	-10.8, 3.1	0.27	-1.8	-6.3, 2.7	0.43
RER at peak exercise, units	-0.05	-0.12, 0.02	0.16	-0.03	-0.08, 0.02	0.24	-0.02	-0.06, 0.02	0.36	0.01	-0.03, 0.05	0.65
Ti/Ttot, %	3.0	1.1, 4.9	0.004	1.3	-0.2, 2.7	0.09	1.5	0.1, 2.8	0.03	0.2	-1.1, 1.5	0.75
Breathing reserve, *%*	7.5	-4.1, 19.2	0.19	0.3	-7.2, 7.9	0.93	5.8	-1.5, 13.1	0.12	5.5	-1.3, 12.2	0.11
Peak minute ventilation, *L/min*	0.7	-19.2, 20.6	0.94	-11.9	-24.7, 0.9	0.07	-44.4	-58.4, -30.5	<0.001	-32.5	-45.9, -19.2	<0.001
Females	-7.9	-29.3, 13.6	0.43	-11.9	-25.0, 1.1	0.07	-24.9	-36.7, -13.1	<0.001	-12.9	-24.6, -1.3	0.03
Males	-0.9	-34.8, 33.0	0.95	-16.7	-34.3, 0.9	0.06	-51.0	-67.7, -34.2	<0.001	-34.3	-48.4, -20.2	<0.001
Distance, *meter*	100	-57, 257	0.19	34	-91, 159	0.59	-225	-354, -96	0.001	-258	-393, -124	<0.001
Females	152	-466, 769	0.50	78	162, 319	0.49	-61	-301, 178	0.59	-140	-286, 7	0.06
Males	57	-73, 188	0.35	-50	-224, 124	0.55	-316	-457, -174	<0.001	-266	-463, -68	0.01
Peak VO_2, *ml/kg/min*	2.0	-3.3, 7.3	0.43	-0.6	-4.5, 3.3	0.76	-6.1	-9.8, -2.4	0.002	-5.5	-9.5, -1.6	0.007
Females	4.0	-10.1, 18.1	0.48	-0.7	-6.4, 5.1	0.82	-2.7	-8.3, 2.9	0.32	-2.1	-7.0, 2.9	0.40
Males	-1.0	-6.9, 4.8	0.70	-1.2	-6.9, 4.6	0.67	-7.4	-11.7, -3.1	0.001	-6.2	-12.1, -0.3	0.04
Peak VO_2, *% of predicted*	1.3	-11.3, 13,8	0.83	-3.4	-12.2, 5.3	0.44	-10.6	-18.2, -3.0	0.007	-7.2	-15.1, 0.8	0.08
Females	9.5	-24.5, 43.6	0.49	-2.4	-16.3, 11.6	0.73	-7.1	-20.5, 6.2	0.28	-4.8	-16.6, 7.0	0.41
Males	-2.3	-13.3, 8.7	0.65	-2.7	-13.5, 8.1	0.60	-14.4	-22.6, -6.3	0.001	-11.7	-22.7, -0.63	0.04

Abbreviations: Diff: difference; RER: respiratory exchange ratio; Ti/Ttot: Inspiratory time/Total inspiratory and expiratory time ratio; VO_2: oxygen consumption.
Breathing reserve is the difference between maximal voluntary ventilation (FEV_1 x 35) and peak minute ventilation as percentage of maximal voluntary ventilation;
95%CI: 95% confidence interval.
p) Independent sample t-test (equal variance not assumed).
Number of subjects: LVCP: n = 13 (5 females), No LVCP: n=12 (7 females), PDA-surgery: n=25 (12 females), EP-born controls: n=30 (17 females), term-born controls: n=36 (13 females). Mean difference = the first mentioned group minus the last-mentioned group.

Supplementary figure 1 Self-reported physical activity among the EP-born participants who underwent neonatal PDA surgery with and without left vocal cord paralysis (LVCP)

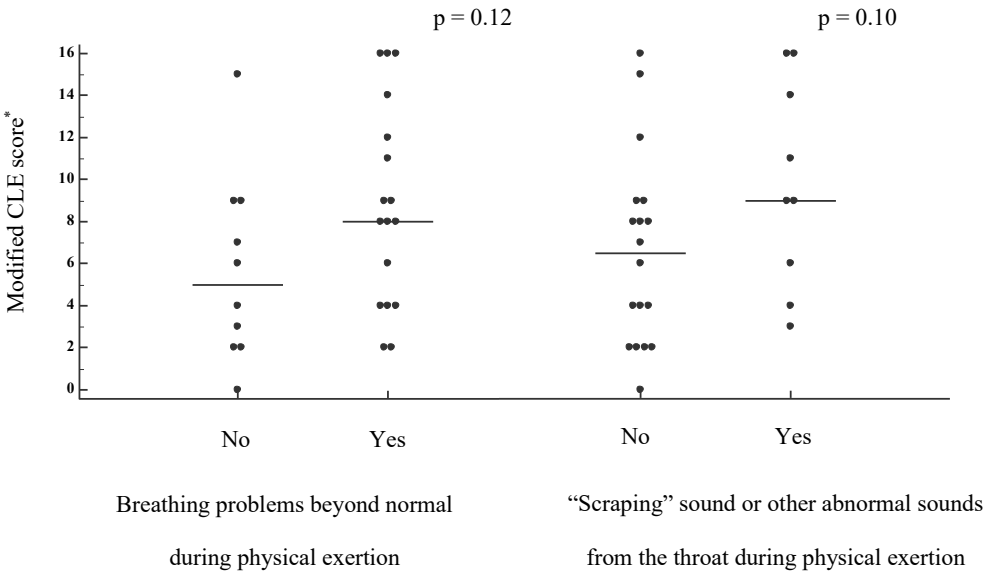


Answer to the self-reported question *"How many hours per week do you attend sports, exercise, or exert yourself so much that you get out of breath and/or sweat?"*

Response rate: No LVCP: n = 13/13, LVCP: n = 14/14,

p) Fisher's exact test

Supplementary figure 2 Comparison of visually assessed laryngeal obstruction during exercise (modified CLE score) according to self-reported breathing symptoms in extremely preterm born adults that underwent neonatal patent ductus arteriosus surgery



*) Higher modified CLE score indicate more laryngeal obstruction

Median values are indicated by vertical lines

p) Mann-Whitney U test

Paper IV

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ORIGINAL ARTICLE
LUNG FUNCTION

Reliability of maximum oxygen uptake in cardiopulmonary exercise testing with continuous laryngoscopy

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ABSTRACT

Aims: A cardiopulmonary exercise test (CPET) is the gold standard to evaluate symptom-limiting exercise intolerance, while continuous laryngoscopy performed during exercise (CLE) is required to diagnose exercise-induced laryngeal obstruction. Combining CPET with CLE would save time and resources; however, the CPET data may be distorted by the extra equipment. We therefore aimed to study whether CPET with CLE influences peak oxygen uptake (V'_{O_2}peak) and other gas exchange parameters when compared to a regular CPET.

Methods: Forty healthy athletes without exercise-related breathing problems, 15–35 years of age, performed CPET to peak exercise with and without an added CLE set-up, in randomised order 2–4 days apart, applying an identical computerised treadmill protocol.

Results: At peak exercise, the mean difference (95% confidence interval) between CPET with and without extra CLE set-up for V'_{O_2}peak, respiratory exchange ratio (RER), minute ventilation (V'_E) and heart rate (HR) was 0.2 (−0.4 to 0.8) mL·kg^{-1}·min^{-1}, 0.01(−0.007 to 0.027) units, 2.6 (−1.3 to 6.5) L·min^{-1} and 1.4 (−0.8 to 3.5) beats·min^{-1}, respectively. Agreement (95% limits of agreement) for V'_{O_2}peak, RER and V'_E was 0.2 (±3.7) mL·kg^{-1}·min^{-1}, 0.01 (±0.10) units and 2.6 (±24.0) L·min^{-1}, respectively. No systematic or proportional bias was found except for the completed distance, which was 49 m (95% CI 16 to 82 m) longer during CPET.

Conclusion: Parameters of gas exchange, including V'_{O_2}peak and RER, obtained from a maximal CPET performed with the extra CLE set-up can be used interchangeably with data obtained from standard CPET, thus preventing unnecessary additional testing.

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Introduction

Exercise-related breathing problems are common, with causes varying from poor physical condition, overweight or de-training, to disease conditions such as respiratory or cardiac disorders [1]. Asthma and exercise-induced bronchoconstriction are important causes of exercise-related breathing problems; however, the significance of exercise-induced laryngeal obstruction (EILO) is increasingly acknowledged [2]. With a prevalence of 5–7% in unselected adolescent populations [3, 4], and even higher in groups where exercise is particularly important [5, 6], EILO is now recognised as an important cause of exertional breathlessness [3, 7, 8]. We know that misdiagnosing exercise-related breathing problems might lead to unfortunate consequences and delay institution of adequate treatment [9–12]. We also know that diagnostic evaluations based solely on patients' symptom descriptions are inaccurate, and guidelines therefore prescribe objective evaluation [13]. Despite good intentions, diagnostic errors are made, often because objective tests are not performed [5, 14–17].

A cardiopulmonary exercise test (CPET) is the gold standard for evaluating symptom-limiting exercise intolerance in patients with suspected respiratory or cardiac disease [18]. Continuous laryngoscopy exercise (CLE) testing is the gold standard for diagnosing EILO and requires flexible video laryngoscopy performed during a maximal CPET [8, 19]. Combining CPET and CLE on a treadmill was first performed by our research group, published in 2006 [20]. This combined set-up has benefits in clinical and scientific situations, enabling comprehensive physiological evaluations of gas exchange, and cardiovascular and respiratory capacities and limitations, in addition to concomitant visual assessment of the larynx [1].

Measurement of maximal oxygen consumption (V'_{O_2}) based on a standard CPET is highly reproducible [21]. The combined set-up of CPET and CLE represents more stress for the patient, adds extra weight, and can introduce air leaks, all of which might influence performance and gas exchange. Mirza *et al.* [22] found no systematic difference between important parameters of gas exchange obtained from bicycle CPETs performed with and without continuous laryngoscopy. We aimed to expand on that knowledge, and conducted a full method comparison study using treadmill exercise, evaluating reliability and the upper and lower limits of agreement between peak oxygen consumption (V'_{O_2}peak) and other parameters of gas exchange obtained from a CPET with and without added CLE equipment.

Material and methods

Subjects and study design

In this method comparison study, a convenience sample of healthy 15–35-year-old athletes participating in endurance training for a minimum of four times per week, were recruited to perform CPET to peak exercise, with and without added CLE set-up, in a randomised order. The two tests were performed 2–4 days apart applying the same computerised treadmill protocol. Except for the modifications required for the CLE test, the equipment and the pre-test preparations were identical. The test personnel consisted of three people, providing instructions and encouragement in similar ways.

At inclusion, all participants completed a questionnaire on past medical history and habits of physical activity and exercise. Subjects who reported breathing difficulties at rest or during exercise, or who had any medical issues (except well-controlled asthma) were not enrolled. Information on the use of nicotine, food intake, hours of nightly sleep, time of previous workout, or any symptoms of illness were obtained for the 24 h preceding both tests.

Pulmonary function

Spirometry was performed on both test days, using a Vyntus PNEUMO spirometer (Vyaire Medical GmbH, Leibnizstrasse, Hoechberg, Germany) according to guidelines [23]. Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) were recorded and reported as raw data and as z-scores calculated by the Global Lung Function Initiate online calculator [24].

CPET

An incremental treadmill (Woodway PPS 55 Med, Weil am Rhein, Germany) test was applied, using a pre-set modified Bruce protocol [25]. Speed and elevation were gradually increased every 60 s from an initial slow walking phase. A facemask (Hans Rudolph Inc., Kansas City, MO, USA) connected the patient to a Vyntus CPX unit powered by SentrySuite software (Vyaire Medical GmbH, Leibnizstrasse, Hoechberg, Germany). After baseline variables were established, subjects ran to exhaustion. Parameters of gas exchange and airflow were measured breath-by-breath and averaged over 30 s.

The test was considered successful when the subjects indicated exhaustion, preferably supported by a plateau in V'_{O_2} and/or the heart rate (HR) response. Duration and completed treadmill distance were recorded. V'_{O_2}, carbon dioxide output (V'_{CO_2}), tidal volume (V_T), respiratory rate (RR) and HR were measured directly, while minute ventilation (V'_E) was calculated from V_T and RR.

CLE test

The CPET part of the CLE test was performed as described above. After application of local anaesthesia (Lidocaine), a flexible fibreoptic laryngoscope (Olympus ENF-V2, Tokyo, Japan) with diameter 3.4 mm was introduced into the pharyngeal space *via* a tight-fit opening in a slightly modified Hans Rudolph facemask and through one nostril (figure 1). The mask was tested for air leaks and the laryngoscope was secured with tape and positioned for a good view of the laryngeal entrance, including supraglottic structures and the vocal folds. The body of the laryngoscope was secured to the head of the test person by custom-made headgear. During the treadmill test, the added CLE equipment allowed for videorecording of the laryngeal inlet (figure 1).

Analysis

Data were reported as means with 95% confidence intervals, ranges or SD for continuous data or counts with percentages for categorical data. Cardiopulmonary exercise data from tests without the CLE set-up were labelled "CPET", whereas data from tests with the added CLE set-up were labelled "CLE". A paired t-test was used to compare mean differences.

An intraclass correlation coefficient (ICC) using a two-way mixed effect model based on single ratings was calculated to assess the absolute agreement of the repeated measurements at peak exercise; V'_{O_2}peak, V'_{CO_2}peak, respiratory exchange ratio (RER), RR, HR, V_T and V'_E. Values >0.6 were considered to indicate good reliability, and values >0.9 to indicate excellent reliability [26]. To assess the reproducibility of the data, the within-subject coefficients of variation (CoV) for the parameters were calculated assuming that the SD was reasonably constant across the concentration intervals.

Agreement between the ergospirometry data produced by the CPET and CLE method was assessed by calculating the SD of the mean difference between the measurements obtained with the two techniques. The SD was used to calculate 95% limits of agreement (LoA) between the two techniques, representing ±1.96 SD of the differences [27]. Results were expressed as values and percentages of the average of the paired differences and visualised in Bland–Altman plots for V'_{O_2}peak, RER and V'_E. We considered 3.5 mL·kg^{-1}·min^{-1} to be the maximum acceptable difference within pairs of peak V'_{O_2} measurements, equivalent to one metabolic equivalent of task. One-sample t-test *versus* zero was used to examine for a systematic bias between the two methods. The differences between the two methods were regressed on their average to test for proportional bias (*i.e.* if the differences were influenced by the numerical size of the measurements). Normal distribution of the differences was verified by a Kolmogorov–Smirnov test.

The criterion for statistical significance was set at $p<0.05$. Statistical calculations were performed using the statistical software SPSS version 25 (IBM SPPS Statistics, Armonk, NY, USA) and MedCalc version 19.5.3 (MedCalc Software Ltd., Osted, Belgium).

We used MedCalc statistical software to determine an appropriate sample size for agreement of peak V'_{O_2} (α values set to 0.05 and power to 90%). A minimum of 31 pairs were required, providing an expected mean difference of 0.4 mL·kg^{-1}·min^{-1}, an expected SD for the mean difference of 1.0 mL·kg^{-1}·min^{-1}, and 95% LoA set to 3.5 mL·kg^{-1}·min^{-1}.

Ethics

The Regional Committee for Medical and Health Research Ethics of the Western Norway Health Authority approved of the study (REC 2014/601). Written informed consent was obtained from all participants. For participants under 16 years, parents also signed the consent.

Results

Of 47 participants, 40 (21 females) successfully completed both the CPET and the CLE test. Their characteristics are given in table 1 and the CPET results are summarised in table 2. Four of the seven incomplete datasets represent participants who were declined further participation because of an asthma exacerbation or for EILO symptoms discovered at the first test, one had difficulties running on the treadmill, one could not find time for the second test, and one participant actively declined to perform the repeat test.

Ergospirometry data obtained with or without the CLE set-up did not differ. The distance completed on the treadmill was 49 m (95% CI 16 to 82 m) longer during CPET than during the CLE test (systematic bias), but there was no proportional bias. For all other parameters, there was no systematic or proportional bias (*i.e.* the data produced by the two methods did not systematically differ from each other), nor were there differences between the measurements influenced by the size of their average.

Table 3 summaries the reliability and reproducibility of the parameters and figure 2 illustrates the agreement for V'_{O_2}peak, V'_E and RER in Bland–Altman plots. For V'_{O_2}peak the mean difference (95%

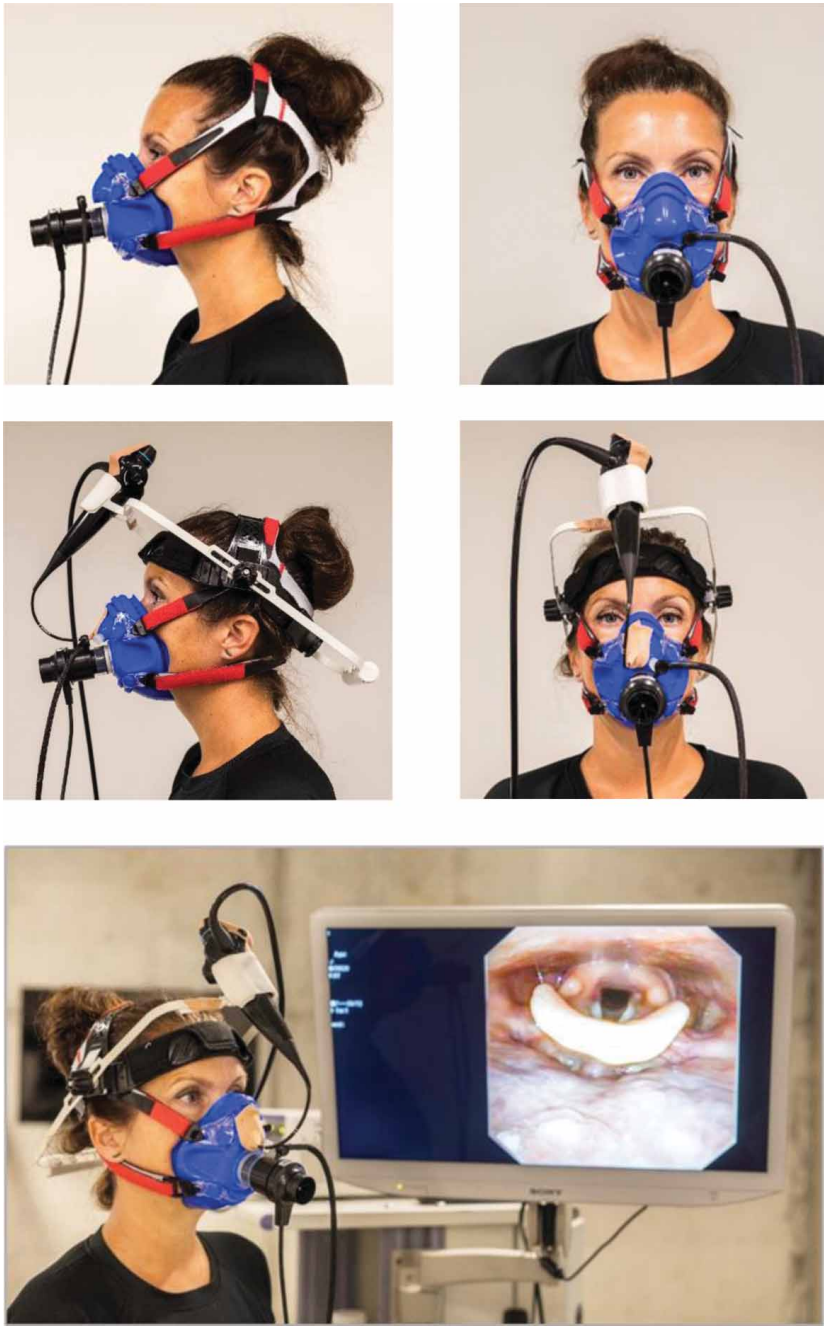

FIGURE 1 Illustration of the set-up for cardiopulmonary exercise test (CPET) with and without continuous video laryngoscopy. The upper left and right images demonstrate the facemask used for ordinary CPET. The middle left and right images demonstrate the modified facemask with a flexible transnasal laryngoscope positioned through a tight-fit opening. A custom-made headgear secures the body of the laryngoscope. The attached transnasal flexible laryngoscope enables video recording of the laryngeal inlet during the maximal exercise treadmill test (bottom image).

TABLE 1 Characteristics of the 40 subjects comparing peak oxygen consumption measured with or without continuous laryngoscopy during cardiopulmonary exercise test on a treadmill

Female sex n (%)	21 (53)
Age years mean (range)	24.8 (15.0 to 35.0)
BMI kg·m^{-2}	22.3±2.3
Smoking n (%)	0 (0)
Exercise	
4–6 days per week n (%)	19 (47.5)
Daily n (%)	21 (52.5)
Asthma n (%)	1 (3)
FVC CPET L	5.12±1.26
FVC CLE L	5.15±1.25
FVC z-score CPET	0.25±0.81
FVC z-score CLE	0.30±0.79
FEV_1 CPET L	4.31±1.32
FEV_1 CLE L	4.20±0.92
FEV_1 z-score CPET	0.05±0.83
FEV_1 z-score CLE	0.07±0.79

Data are presented as mean±SD, unless otherwise stated. BMI: body mass index; FVC: forced vital capacity; CPET: cardiopulmonary exercise test; CLE: continuous laryngoscopy during exercise; FEV_1: forced expiratory volume in 1 s.

LoA) was 0.2 (±3.7) mL·kg^{-1}·min^{-1}, and the ICC was excellent with a low CoV (table 3 and figure 2). For V'_E at peak exercise the mean difference (95% LoA) was 2.6 (±24) L·min^{-1}, the ICC was excellent, and the CoV was low. For RER, the agreement was good and the ICC was fair with a low CoV (table 3 and figure 2).

Discussion

This is the first study to establish the LoA between parameters of gas exchange obtained during maximal cardiopulmonary treadmill exercise with and without concurrent laryngoscopy, performed in physically active and healthy subjects. The study indicates that the CLE equipment does not disturb the CPET measurements. CPET and CLE tests are time- and resource-consuming for patients and healthcare providers. Combining the two saves time and ensures that advanced patient evaluation can be performed at lower personal and financial costs.

Our findings are consistent with the only similar study comparing CPET with and without CLE; however, the other study by MIRZA *et al.* [22] was performed in sedentary or moderately physically active individuals with EILO, using a cycle ergometer. They found a mean (95% CI) difference in V'_{O_2}peak of 22 (−125 to 81) mL·min^{-1}, compared to our results of 11 (−33 to 56) mL·min^{-1}. MIRZA *et al.* [22] did not report the degree of expected agreement between the gas exchange parameters obtained with the two methods.

TABLE 2 Ergospirometry data for the 40 participants obtained from cardiopulmonary exercise tests performed without and with added CLE test set-up

Parameter	CPET without CLE		CPET with CLE		Difference	
	Mean	SD	Mean	SD	Mean	(95% CI)
V'_{O_2}peak mL·min^{-1}	3818	873.8	3806	883.4	11.4	(−33.5, 56.2)
V'_{O_2}peak mL·kg^{-1}·min^{-1}	54.9	6.3	54.7	6.6	0.22	(−0.40, 0.83)
V'_{CO_2}peak mL·min^{-1}	4618	1016	4565	1006	53.1	(−25.9, 132.0)
V_T L	2.61	0.65	2.61	0.62	0.005	(−0.08, 0.071)
V'_E L·min^{-1}	142.3	33.1	139.7	34.2	2.58	(−1.33, 6.49)
HR beats·min^{-1}	186	8.7	185	9.0	1.4	(−0.8, 3.5)
RR breaths·min^{-1}	55	9.3	54	10.0	1.2	(−1.5, 4.0)
RER units	1.21	0.05	1.20	0.05	0.01	(−0.007, 0.027)
Distance m	1199	219	1150	210	49	(15.7, 82.0)

CLE: continuous laryngoscopy during exercise; CPET: cardiopulmonary exercise test; V'_{O_2}peak: oxygen consumption at peak exercise; V'_{CO_2}peak: carbon dioxide production at peak exercise; V_T: tidal volume; V'_E: minute ventilation; HR: heart rate; RR: respiratory rate; RER: respiratory exchange rate.

TABLE 3 Reliability and reproducibility of the ergospirometry data obtained for the 40 participants performing cardiopulmonary exercise test with and without CLE test set-up

Parameter	Agreement	Lower LoA	Upper LoA	ICC	(95% CI)	WS-SD	CoV %
V'_{O2}peak mL·min^{-1}	11.4	−263	286	0.988	(0.977, 0.993)	98	2.6
V'_{O2}peak mL·kg^{-1}·min^{-1}	0.2	−3.5	4.0	0.957	(0.920, 0.977)	1.3	2.5
V'_{CO2}peak mL·min^{-1}	53.1	−431	537	0.970	(0.943, 0.984)	176	3.8
V_T L	0.0	−0.47	0.46	0.933	(0.876, 0.964)	0.16	6.3
V'_E L·min^{-1}	2.6	−21.4	26.5	0.933	(0.877, 0.964)	8.7	6.2
HR beats·min^{-1}	1.4	−11.6	14.3	0.720	(0.532, 0.841)	4.7	2.5
RR breaths·min^{-1}	−2.5	−19.9	15.0	0.614	(0.375, 0.777)	6.0	11.1
RER units	0.01	−0.09	0.11	0.502	(0.233, 0.700)	0.04	3.1

CLE: continuous laryngoscopy during exercise; LoA: limit of agreement; ICC: intraclass correlation coefficient; WS-SD: within-subject SD; CoV: coefficient of variation; V'_{O_2}peak: oxygen consumption at peak exercise; V'_{CO_2}peak: carbon dioxide production at peak exercise; V_T: tidal volume; V'_E: minute ventilation; HR: heart rate; RR: respiratory rate; RER: respiratory exchange rate.

We opted to apply a treadmill protocol, aiming to achieve the highest possible effort of the subjects. Treadmill exercise has proven feasible in subjects not familiar with exercise testing in general [28] and it is our experience that children and adolescents more often exercise to exhaustion on a treadmill than on a cycle ergometer. Moreover, running involves larger muscle masses and leads to a greater stress on the organ systems mediating the exercise response, generally leading to 5–10% higher maximal oxygen consumption [29, 30]. This might be of importance in athletes, and in some patients where abnormalities may occur only at high metabolic demands, which could be the case for patients with symptoms resembling EILO [29].

V'_{O_2}peak is the most important CPET parameter for determining cardiorespiratory fitness and it is commonly used as a primary end-point for studies to determine the effect of therapeutic interventions or training programmes [31]. DECATO *et al.* [32] provide an overview of studies reporting repeatability of CPET variables both for normal subjects and chronically ill patients. For V'_{O_2}peak, the CoV ranges from 3.0% to 13% [33, 34] and large studies using highly consistent exercise test methodology found CoVs of 4.9 to 5.1% [32, 35]. Heterogeneities between studies represent technical errors, technicians with varying experiences, and different exercise protocols in addition to biological variation [36]. In our study there was no systematic bias favouring any of the two methods, and the CoV of V'_{O_2}peak measurements was only 2.5% (*i.e.* a value below what is reported for repeat CPETs). This steadiness may be due to our test

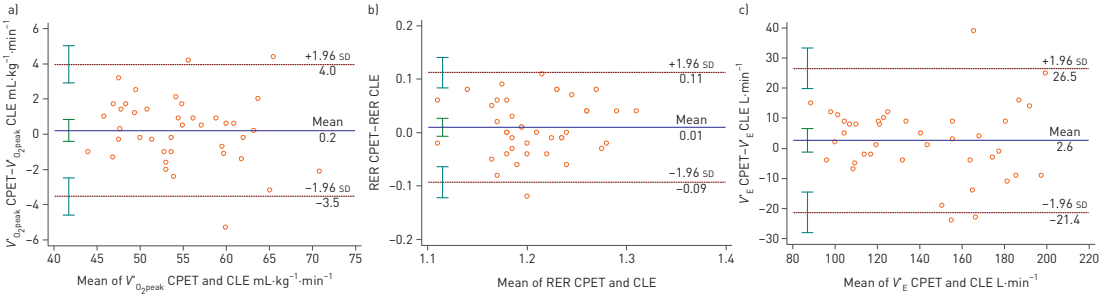

FIGURE 2 Agreement between peak oxygen consumption (V'_{O_2}peak), respiratory exchange ratio (RER) and minute ventilation (V'_E) obtained from cardiopulmonary exercise testing (CPET) and continuous laryngoscopy performed during exercise (CLE) test. The horizontal lines depict the mean difference between the variables obtained with the two methods, whereas ±1.96 SD of these differences represent 95% limits of agreement between the two methods. The 95% confidence intervals for the mean, the upper limit of agreement and the lower limit of agreement are indicated by vertical lines. The figures given below in the brackets are the mean difference and the upper and lower limits of agreement, expressed as percentages of the mean of the CPET and CLE value. a) Agreement between V'_{O_2}peak, expressed as mL·kg^{-1}·min^{-1}, obtained from CPET and CLE tests. The mean difference was 0.2 mL·kg^{-1}·min^{-1} (0.4%), the upper limit of agreement was 4.0 mL·kg^{-1}·min^{-1} (7.0%), and the lower limit of agreement was −3.5 mL·kg^{-1}·min^{-1} (−6.2%). b) Agreement between RER obtained from CPET and CLE test at peak exercise. The mean difference was 0.01 units (0.7%), the upper limit of agreement was 0.11 units (9.2%), and the lower limit of agreement was −0.09 units (−7.8%). c) Agreement between V'_E obtained from CPET and CLE test at peak exercise. The mean difference was 2.58 L·min^{-1} (2.2%), the upper limit of agreement was 26.5 L·min^{-1} (18.3%), and the lower limit of agreement was −21.4 L·min^{-1} (−13.9%).

population, consisting of athletes who conceivably are more used to repeatedly performing to their peak exercise capacity than average sedentary individuals.

The CoV of the parameters V'_E, RER, and HR in the present study were generally consistent with or lower than previous reports from repeatability studies of CPET without CLE [32]. The ICCs for V'_E and HR were excellent and good, respectively. The ICC for RER was not as good as the other parameters, which may be explained by the diurnal variation of this parameter as the participants were not scheduled for testing at the same hours of the day [32]. The mean completed distance was 49 m longer for the test without the CLE set-up, yet achieving the same V'_{O_2}peak. This result could be explained by the added weight and higher work of breathing with one nostril occlude by the laryngoscope, although this assumption is uncertain, and we cannot provide a good explanation. Regarding peak V'_E, LoA was relatively wide and in the area of 15% of its mean value, which is in line with studies testing repeatability of CPET [32]. Peak V'_E is included in the calculation of a patient's breathing reserve, which is used to identify ventilatory limitation to exercise. Based on the result from this study, caution should be exercised if a ventilatory limitation to exercise is established solely on the interpretation of a reduced breathing reserve.

CPET is considered the gold standard for evaluating symptom-limited exercise tolerance in patients with pulmonary and cardiac disease [18]. Although response patterns obtained from CPET are not necessarily disease-specific, they nevertheless contribute to the diagnostic process of narrowing down the spectrum of differential diagnoses. Normal CPET response patterns are usually taken as evidence against significant involvement of these systems in exercise limitation. Combining CPET with the CLE test is valuable in several ways. The most obvious advantage is that exercise-induced changes of the laryngeal configuration can be evaluated against corresponding changes of gas exchange parameters. This can be of value in the understanding of individual patients' limitations, as well as facilitate a better understanding of the phenomenon of EILO in research, such as providing outcome measures in intervention studies that aim to improve EILO. Moreover, CPET data will identify if patients reach their maximum level of effort and can serve to identify abnormalities in the oxygen transport pathways, irrespectively of obstructions in the larynx. Lastly, if no signs of abnormalities are revealed, the CPET data inform that the patient's dyspnoea is not likely to be associated with an abnormal physiological limitation, but instead consistent with the actual physical fitness of the tested individual.

Finding a normal V'_{O_2}peak may be helpful in providing reassurance to patients and prevent unnecessary subsequent testing and evaluations. However, it is important to bear in mind that CPET results should be interpreted based on expected values for the population under investigation [29, 37]. Therefore, it is important to ensure that the gas exchange parameters obtained from a CLE test are correct also in physically active individuals, as shown by this study.

Strength and limitations

The major strengths of this study were the randomised crossover design and the relatively high number of participants performing endurance training at a high level. Measuring V'_{O_2}peak may be influenced by a learning effect, and performing the tests in randomised order controlled for this possible bias [29].

All our participants were highly physically active performing endurance training at least four times per week with no reports of breathing problems. Their familiarity with high-level training and performance likely reduced the variation between the two tests. Moreover, other studies testing reproducibility of V'_{O_2}peak have used shorter test protocols and longer "between-test" periods of up to 30 days compared to our maximum of 2 weeks [32].

We did not systematically collect information on previous experiences with exercise testing, flexible laryngoscopy, or CLE testing prior to inclusion. This is a limitation to the study as familiarity with the test situation can influence the results. In the records from our test laboratory, we found that prior to the study, six subjects had performed a CPET test and none had performed a CLE test. The distance to the next cardiopulmonary laboratory capable of performing a CLE test is 600 km. Thus, we find it unlikely that any of these healthy participants had performed a CLE test prior to this study.

Testing only healthy athletic subjects without respiratory complaints, challenges the validity for patients who undergo cardiopulmonary exercise testing for reasons other than EILO. On the other hand, this limitation represents a strength in the context of testing patients with EILO, as EILO is common in athletes and physically active individuals [5]. The test personnel were not technically prevented from access to previous results, and access to such knowledge could in theory have influenced their level of encouragement during the second test. However, the test personnel were skilled and experienced researchers who did in fact not access the previous test results. We did not collect information on how the added laryngoscope influenced perceived dyspnoea or discomfort during test, and we did not use a Borg score or other dyspnoea or discomfort scores. Ultimately, dyspnoea or breathing difficulties during exercise

are the main reason for performing a CPET with CLE, and future studies should explore the added discomfort imposed by the extra necessary gear.

The 95% LoA between V'_{O_2}peak obtained from CPET with and without CLE was 0.2 ±3.7 mL·kg^{-1}·min^{-1}, which was slightly higher than the 3.5 mL·kg^{-1}·min^{-1} that we had considered clinically relevant. This was due to the SD of the mean difference being larger than expected, which could have been moderated by including more participants. However, inclusion was complicated by active young people with tight schedules, a busy exercise test laboratory, and a test protocol that prescribed replicate testing within 2 weeks.

In conclusion, V'_{O_2}peak and most of the other ergospirometry data obtained from a CLE test can be used interchangeably with data obtained from a standard CPET in athletes and highly physically trained individuals. Thus, we recommend performing CPET with CLE set-up, if available, when assessing patients with unexplained exertional breathing problems.

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Data availability: In accordance with the approval granted for this study by The Regional Committee on Medical Research Ethics and The Norwegian Data Inspectorate, the data files are stored securely and in accordance with the Norwegian Law of Privacy Protection. A subset of the data file with anonymised data can be made available to interested researchers upon reasonable request to H. Clemm, providing that Norwegian privacy legislation and the General Data Protection Regulation are respected, and that permission is granted from The Norwegian Data Inspectorate and the data protection officer at Haukeland University Hospital.

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